1958

Quantitative and Qualitative Behavioral Changes in the Rhesus Monkey After Lesions of the Caudate Nucleus.

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QUANTITATIVE AND QUALITATIVE BEHAVIORAL CHANGES IN THE RHESUS MONKEY AFTER LESIONS OF THE CAUDATE NUCLEUS

A Dissertation

Submitted to the Graduate Faculty of the
Louisiana State University and
Agricultural and Mechanical College
in partial fulfillment of the
requirements for the degree of
Doctor of Philosophy

in

The Department of Psychology

by
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A.B., University of Kansas, 1950
M.S., Louisiana State University, 1955
June, 1958

ACKNOWLEDGMENT

Many people have aided the examiner by giving freely of their talents and support. Especial thanks are due to a number of people who have taken time from their busy schedules to give material aid and helpful advice.

Dr. Thomas W. Richards, Chairman of the Dissertation Committee, has been very kind in the careful and thoughtful supervision he has given to the details of experimental design, statistical analysis of results, and techniques of good scientific writing.

Dr. Louis A. Toth, acting Chairman of the Department of Physiology, made this work possible by making the resources of the department available to the examiner.

The author wishes to thank Dr. George D. Davis who performed the surgical operations, gave many hours of his time in counsel, and served as a source of inspiration and example.

Many thanks are due to Dr. John Moossy who evaluated some of the histological material. Miss Catherine Ingenhutt prepared a set of serial brain sections which were of great value.

Many thanks are due to Mr. Joseph August who worked long hours preparing high quality histological slides. Mr. James Morris has also been much help in the care and management of the monkeys.

Dr. Henry Higman has helped greatly by recording and interpreting electroencephalograms of some of the test animals.

The National Institute of Neurological Diseases and Blindness aided the work by financial support through Grant B-874. Also, the research committee of the LSU Medical School has given funds which were helpful to this study.

Finally, I wish to thank my wife, Lois, for the help she has given my efforts to write a clear manuscript and for the patience she has shown with me while this experiment was in progress.

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ABSTRACT

This experiment is an investigation of the behavioral changes occurring following lesions of the caudate nucleus. Surgical lesions of the caudate nucleus and other structures were produced in five rhesus monkeys. Quantitative and qualitative disturbances in behavior were observed after operation. Drugs known to have an effect on the central nervous system were used in further evaluation of post-operative behavior. Finally, pathological confirmation of the location and dimensions of the surgical lesions was ascertained.

The conclusions of the present experiment are as follows:

1. Restricted bilateral caudate lesions are followed by a specific loss in learned abilities.

2. Caudate lesions produced no change in color discrimination ability, while delayed response ability is impaired.

3. Unilateral lesions of the caudate result in a well defined partial loss of delayed response ability.

4. The excitant drug Phenidylate restores delayed response performance. The tranquilizing agent reserpine also restores delayed response, although not as effectively.

5. Caudate lesions produce a defect in memory which is followed by difficulty in performing tasks where forced time delay is involved.

6. Correlation between anatomical damage of the caudate and loss of delayed response abilities is good.

INTRODUCTION

In the past several years much attention has been given to the function of the frontal lobes in man and lower animals. Mental patients who have received frontal lobotomies have been described as deficient in memory for recent events, short in attention span, flattened in affect, and largely indifferent to the demands of the external environment which formerly disturbed them.

The procedure of frontal lobotomy in man originated directly from experimental work with primates, notably that of Jacobsen who found that lesions in the frontal lobes of monkeys were followed by serious changes in behavior requiring retention of response sets over a forced period of delay. The effect of Jacobsen's work was to highlight the significance of the delayed response changes specifically and to create the impression that the crucial damage to the brain was "frontal lobe" and not some more discrete focus of damage.

The person familiar with the literature of delayed response testing in frontal lesion experiments realizes that the various investigators in the field are in great disagreement. The correlation of psychological test behavior with anatomical abnormalities is a subject much debated among various examiners. It is the interpretation of some workers that monkeys fail the delayed response problem because of abnormalities in the subject's response to the significant

test cue and not because of memory defects. There is no agreement between groups of workers as to the limits of the frontal lesions necessary to produce these effects. Most workers feel that the lesions must be cortical and must involve both hemispheres of the brain.

A recent study by Rosvold and Delgado (1956) found that lesions of the caudate nucleus are followed by a loss of ability to perform the delayed alternation test. This finding suggests that damage to the caudate nucleus may play a crucial part in the loss of delay abilities found in monkeys with frontal lesions. The caudate nucleus is a structure which is often unintentionally damaged in animals experimentally and in human frontal lobe surgery. In addition, as a part of the heavily vascular basal gangliar complex, the caudate is often involved in cerebral vascular accidents and many other neurological disorders.

For these reasons, there exists, in the minds of many people interested in the several disciplines involved with the nervous system, a desire to know more about the behavioral correlates of the caudate nucleus. The present study has been designed to widen knowledge in this area. This has been done as follows:

1. The investigator acquired thorough familiarity with the behavior of a group of normal rhesus monkeys, using both quantitative testing and qualitative observation.

2. Lesions of the caudate nucleus and other structures were produced in these monkeys.

3. Following operation, behavioral data on the animals was then gathered.

4. Drugs known to have an effect on the central nervous system were used in the further evaluation of post-operative behavior.

5. The exact location and dimensions of each surgical lesion was ascertained.

The results of each of these steps are reported in this dissertation. Finally, these data are considered together with other contributory information on the experimental animals, in an attempt to present to the reader a picture of the total behavior which follows proven damage to the caudate nucleus.

CHAPTER I

REVIEW OF THE LITERATURE

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REVIEW OF THE LITERATURE

FRONTAL LESIONS AND DELAYED RESPONSE DEFICIT

The inability to respond correctly to previous stimuli even after minimal delays has been a constant and striking symptom of ablation of the frontal granular cortex in monkeys. The studies of C. F. Jacobsen and his colleagues (1931, 1935, 1936, 1937) have become classics in the field. In his work, monkeys were shown food hidden under the right or left of two cups. Then the animals were forced to wait for several seconds before they could reach for a cup, remove it, and get food. Jacobsen's findings were very simple. Normal monkeys could delay for thirty seconds without difficulty and then select the correct cup. Monkeys with bilateral removals of the frontal lobes, however, could not solve the delayed response test if required to wait more than one or two seconds. Indeed, such animals often experienced a complete loss of ability to choose correctly after delay. Jacobsen and Elder (1936) were interested in whether other areas of the brain are involved in the capacity to make delayed reactions. They showed that bilateral lesions of the temporal lobes resulted in no impairment of ability to perform this test. In another paper, Jacobsen and Haslerud (1936) presented evidence that lesions of the motor cortex did not specifically impair

delayed reaction tasks. It was in this way that behavioral tests of the delayed response type came to indicate deficits resulting from frontal, pre-motor lesions. It should be pointed out that later work still to be reviewed has modified some of the conclusions gained from these first studies.

DEFINITION OF THE LIMITS OF THE DELAYED RESPONSE TEST

Since the original studies of Jacobsen, much subsequent literature on delayed response has been concerned with defining the behavioral limits of the test more exactly. Also, many special experimental conditions have been studied which have proved effective in allowing operated animals to perform the delayed response. Jacobsen advanced the theory that prefrontal animals cannot do the delayed response because the operation has impaired their recent memory. To quote from Jacobsen's 1936 paper:

> "Bilateral injury to the frontal association areas in primates results in severe deterioration of certain modes of behavior. More specifically, operated animals are unable to remember after a lapse of a few seconds under which of two cups food is concealed. . . . It is as if 'out of sight, out of mind' were literally applicable. The temporal organization so characteristic of normal behavior is greatly reduced, if not entirely lacking.
>
> Deterioration, however, is not generalized; the loss is specific rather than global. . . . the nmenonic influence of immediately past experience is lacking."[1]

Finan (1939) put this interpretation to test. He ran

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[1] Jacobsen, C. F., 1936. Pp. 51 and 52.

prefrontal monkeys in several kinds of learning problems where memory traces had to last for some time in order for the animal to make a correct choice. In one problem, monkeys had to shuttle from one grill to another several seconds after a signal was presented. In another one, they learned a temporal maze in which one route took a much longer time than the other. Both prefrontal and normal animals solved the tasks, even though prefrontal animals were not able to do the delayed response. Finan concluded that the prefrontal animals had no basic quantitative disability in holding memory traces.

Another explanation for the difficulties experienced by prefrontal animals in the delayed response task could be an inability to form the "meaningful connection." Frontal operated monkeys seem not to notice where food is being placed during the cue-presentation period, and therefore have nothing to remember in the delay period. Finan (1940) published a study in which pre-delay performance was rewarded. With this technique, Finan was able to restore delayed response in frontal animals to preoperative levels. This finding indicates difficulty in the pre-performance period and not in the period of delay. Malmo (1942) reports success in delayed response in bilateral frontal animals when they were tested in the dark under conditions designed to keep distractions to a minimum during the pre-performance cue period.

Other work supports the conclusion that conditions during the cue period are important in delayed response performance. Carpenter and Nissen (1934) trained a single chimpanzee to do the delayed response. They incorporated into the standard apparatus an opaque grill 72 inches wide. The cue cups were mounted so that they could be converged and diverged at the will of the examiner. Increasing the distance between cue cups improved delayed response test performance. Interference with the visual field, using the screen, lowered accuracy. The time of delay was also correlated with accuracy. Mishkin and Pribram (1956) studied the effects of variations in the delayed response cue. Using several variants of cue presentation, these investigators found that positional vs. non-positional placement of the cue was important. They concluded that conceptions of one-trial learning and recent memory are not sufficient to explain the frontal operate's difficulty with delayed response. The impairment of the frontal operate is related not only to the period of delay but also to the nature of the pre-delay cue. Pribram and Mishkin (1955) did a similar study on object alternation in the frontal lesioned monkey. Their conclusion was the same as in the 1956 delayed response study, i.e. that the success of the frontal operate in tests involving delay depends in part on the distinctiveness of the original cue. Simpson and Harlow (1944) report a study in which normal rhesus monkeys were trained to do a

number of delayed response-type tasks, some of which involved matching to form and others which involved matching to color. From the learning data, they conclude that the differential attributes of the delayed response situation are to be found in the nature of the original stimulus, and also in terms of the complexity of the "signs" that come to be associated with food.

QUALITATIVE VARIANTS OF THE DELAYED RESPONSE TEST

Several papers have been concerned with the theoretical nature of the delayed response test. Here, the attempt has been made to formulate theory as to the nature of the learning process involved in delayed response tests. Cowles (1939), using 39 albino rats, discusses delayed response as a series of nonsuccessive discrimination trials. Cowles felt that delayed response involves a transfer problem in learning rather than symbolic behavior. In a later theoretical paper, Cowles (1941) relates delayed response to ordinary noncomplex discrimination learning. Simple discrimination learning centers about the acquisition of a single habit to the exclusion of others, while delayed response requires the current acquisition and operation of two or more habits. Delayed response is seen as a higher order task which is identical to other simple discrimination tests, except for the magnitude of difficulty. To reason from Cowles' work, frontal operates may fail delayed response because of a generalized decrease in intellectual

ability, instead of a loss in some specific capability. Evidence for such a conclusion may be inferred from studies of other types of behavioral tests which do not suffer complete loss of performance following frontal ablation. Harlow and Dagnon (1942) dealt with problem solving ability of monkeys following bilateral prefrontal lobectomy. Following operation, animals learned a series of discrimination and reversal problems at a slower rate and with more errors than did a comparable group of unoperated controls. Harlow and Spaet (1943) found that monkeys with ablations of the frontal association areas were uniformly inferior in a multiple matching-from-sample delayed response test, even though they indicated ability to do the task.

THE IMPORTANCE OF INDIVIDUAL AND SPECIES DIFFERENCES

Individual differences between animals and between species are an important consideration in delayed response performance. There has been almost no mention in the literature to date about individual differences in animals, beyond the fact that different subjects require different numbers of trials to reach a given criterion of performance. However, several papers have dealt with species differences. Harlow, Vehling, and Maslow (1932) studied 24 different primate species using delayed response from 0-60 seconds delay. The conclusion is reached that the delayed

response is a task of which there is some capacity in all primates, differing only in degree. Harlow (1932) studied eighteen old world monkeys and found an increase in ability from the catarrhine monkeys to the baboon.

THE INFLUENCE OF DRUGS ON TEST PERFORMANCE

A study by Wade (1947) is evidence for the effect of drugs on delayed response performance. In a series of prefrontal animals, she was able to restore delayed response performance without pre-delay reinforcement by administering light sedative dosages of either Nembutal or Dial. With this technique, Wade reported successful delays of 25 seconds in animals otherwise unable to do the delayed response. She also found that one of her monkeys permanently retained ability to do delayed response following medication. Pribram (1950) achieved similar results in two Chacma baboons who had been subjected to bilateral frontal lobotomy. Two animals in this study showed a low level of performance in the delayed response test for six months following operation, under normal conditions of food intake and temperature. Pribram reports that the following conditions significantly improved test performance: intramuscular injection of Nembutal in approximately one-half the anesthetic dose, intramuscular injection of 0.25-0.50 unit of insulin per kilogram of body weight, a reduction of the environmental temperature by 15-20 degrees centigrade for three hours before testing, and fasting for 48-60

hours before testing. Benzedrine (5mg.), elevation of the environmental temperature for three hours before testing, and prefeeding immediately before testing all resulted in a few chance trials or in complete refusal to test.

The findings of Wade and Pribram are not in agreement with those of Blum, Chow, and Blum (1951). These investigators found Nembutal and Benzedrine ineffective in restoring delayed response performance in monkeys with ablations of the frontal granular cortex. They found that post-operative time gave greater improvement than any drugs used. One of the contaminating factors in this study was the low preoperative criteron of satisfactory learning performance. Blum, Chow, and Blum used a plateau in the learning curve as evidence of maximal learning. This resulted in a criterion of 66% correct in 500 trials, which is considerably below the level used by most investigators to signify satisfactory preoperative learning. The low initial criterion may have served to mask effects of post-operative performance levels under the several conditions of the experiment as distinct from those due to insufficient learning of delayed response initially.

The work of Wade and Pribram is evidence for the conclusion that prefrontal animals have not lost a basic ability or memory trace, but are merely impaired in performance because of difficulties in the pre-delay period.

The experiments on pre-delay reinforcement and cue conditions may also be interpreted in this way.

LESION STUDIES

The study of the delayed response test using the ablation technique has been concerned with finding the "critical foci" mediating delayed response behavior. The work of Jacobsen and his associates was limited in general to rather gross frontal ablations, which were followed by a deficit in delayed response performance. Although Jacobsen's findings have been confirmed many times, it is possible, apparently, for some monkeys with such lesions to solve the delayed response. Campbell and Harlow (1945) have done a study of six bilateral prefrontal lobectomized monkeys in which two animals were eventually able to solve the delayed response problem when the examiners used a technique similar to Jacobsen's. Campbell and Harlow conclude that delayed response performance is related to post-operative recovery time, previous experience with the test, and to the extent of the lesions. Blum (1948) reports that spatial delayed response was preserved in two chimpanzees after bilateral prefrontal lobectomy involving areas 6 and 8 of Brodmann. Jacobsen (1936) did a monkey study which involved unilateral removal of a frontal lobe followed by a second equal lesion to the contralateral side. Unilateral ablation had no effect on delayed response, while

bilateral lesions were followed by impaired test performance. Meyer, Harlow, and Settlege (1951) trained twelve rhesus monkeys in the delayed response. The post-operative delay possible extended up to 40 seconds for unilateral frontal animals, while bilateral animals experienced complete loss of delayed response performance.

Other areas of the cerebral cortex have been explored in lesion studies aimed at finding the focus of delayed response deficit which occurs after operation. Breshaw, Barrera, and Warden (1934) reported that unilateral removal of the post-central convolution followed later by a second equal contralateral lesion had no effect on delayed response behavior; based on the fact that post-operative animals continued to learn as a function of trials.

A number of studies by Pribram and his group have implicated the lateral surface of the frontal lobes, anterior to the arcuate sulcus, in delayed response deficit. Pribram, Mishkin, Rosvold, and Kaplan (1952) studied 32 guinea baboons trained on delayed response and a discrimination test. The animals were divided into three groups and received different surgical treatment. Group I was subjected to resection of the dorso-lateral frontal cortex. Group II had a resection of the ventro-medial frontal cortex. Group III was a control. The dorso-lateral resection was followed by the greatest delayed response deficit. The integrity of the dorso-lateral frontal cortex

was found necessary for delayed response performance. Pribram (1955) found delayed response deficit following lesions to the frontal eye fields around sulcus arcuatus.

Blum (1952) trained six macaca mulatta monkeys on the delayed response and then subjected each of them to different frontal-cortical lesions, i.e. complete prefrontal, dorsal-frontal, midlateral-frontal, and ventral-frontal. Only the ventrolateral animal achieved delayed response up to 30 seconds, while the three animals with midlateral-frontal lesions performed at chance. From the data, Blum concludes that the midlateral frontal cortex serves as the focus of delayed response ability. Mishkin (1957) trained ten rhesus monkeys in delayed alternation, a type of behavioral test which has been considered equivalent to tests of the delayed response type. He subjected each of them to one of several different types of frontal cortical lesions. Two animals received ventral-frontal lesions, extending from the ventromedial to the ventrolateral edge of the frontal lobe. The lateral surface was then divided into three subdivisions. Two animals received inferior-frontal lesions, extending from the ventrolateral edge of the lobe to the inferior lip of sulcus principalis. Four animals received midlateral-frontal lesions which included the lips and banks of sulcus principalis. Finally, two animals received superior-frontal lesions, extending from the superior

lip of sulcus principalis to the longitudinal fissure. Post-operatively, the monkeys were tested for retention of the delayed alternation habit. The four midlateral-frontal animals performed at near chance level, at a poorer level than the other monkeys in the series. In one case, a mid-lateral lesion produced a deficit that was as severe and longlasting as that following anterior frontal lobotomy. Mishkin found support for the contention of Blum and Pribram that the midlateral frontal cortex, in the area of sulcus principalis, is the focal cortical area serving de-layed response behavior in the monkey.

DEFICITS FOLLOWING SUBCORTICAL LESIONS

Recently, several investigators have become interested in the role of certain subcortical centers which are known to project to the frontal lobes. Wade (1952) has provided evidence that the essential connections of any focal frontal area which mediates delayed response behavior are with subcortical centers via projection fibers, and not with other cortical areas via short association fibers. This interpretation came from comparison between the ef-fects of lobotomy and circumsection of frontal lobe cortex, the former producing severe impairment of delayed response, the latter producing no effect.

Two subcortical structures, the thalamic nucleus medialis dorsalis and the caudate nucleus in the corpus

striatum are known to have projections to the frontal cortex. In the case of the thalamic nucleus, data from retrograde degeneration studies indicate that the central parvicellar region of n. medialis dorsalis projects to the cortex along sulcus principalis (Walker, 1938, and Pribram, Chow, Semmes, 1953). Chow (1954) trained a series of monkeys to do delayed response and then subjected them to stereotaxic lesions in the parvicellar region of n. medialis dorsalis, as well as other thalamic areas. No delayed response deficit followed these lesions. Peters, Rosvold, and Mirskey (1956) confirmed these results. They found that thalamic lesions, which were similar to Chow's, had no effect on delayed response behavior in the rhesus.

Mettler, Hovde, and Grundfest (1952) have recorded activity in the frontal cortex following stimulation of the caudate nucleus. They described the responsive areas as corresponding to areas 10 and possibly 11 of Brodmann. Evidence for caudate-frontal projection is also found in the work of Harmon, Tankard, Maleva, Hovde, and Mettler (1954) in the report of shrinkage and loss of cells in the caudate nucleus following frontal ablation. It can also be suggested that the results in this study (and in all the behavioral studies involving removals of lateral-frontal cortex) might be due to direct and circulatory damages to the caudate nucleus. Such damages are extremely difficult

to avoid in the normal surgical procedures. Rosvold and Delgado (1956) provide evidence that the caudate nucleus plays an important role in the delayed alternation test. They trained 14 rhesus monkeys in delayed alternation and also in a discrimination task. With implanted electrodes, they observed behavior on these two tests during stimulation and after electrocoagulation of the caudate nucleus. Changes in activity and gastrointestinal disturbances followed destruction of the caudate nucleus and putamen. Electrocoagulation of tissue in the head of the caudate nucleus, but not in any other structure in the corpus striatum (nor in white matter anterior to the corpus striatum) impaired delayed alternation performance. Caudate stimulation and destruction was accompanied by delayed alternation performance at about chance accuracy, while the non-caudate animals maintained criterion (90% correct) performance on delayed alternation while being stimulated in other brain areas. Rosvold and Delgado make the following interpretation of their results:

> "The results of this study thus suggest that the delayed alternation deficit, changes in activity, and gastrointestinal disturbances, which frequently follow prefrontal lobotomy or ablation of frontal cortex and which are usually ascribed to damage to the cortical projections from the thalamus, are due instead to damage to the corpus striatum, particularly the caudate nucleus and its cortical projections."

Rosvold and Delgado were thus able to produce a large deficit in test performance using subcortical lesions which

were intended to be small and discrete.

SUMMARY

The results of a series of papers dealing with the delayed response test have been presented. The early work of Jacobsen and his associates has led to the conclusion that frontal lobe ablation produces delayed response deficit in monkeys. Jacobsen felt that this deficit resulted from a qualitative and specific disability in immediate recall. A summarization of several experiments (which have been reviewed) dealing with lesion studies aimed at finding the "critical foci" for delayed response abilities is as follows:

SUMMARY OF DELAYED RESPONSE EXPERIMENTS

AUTHORS	ANIMALS	SURGERY	TESTS	RESULTS
(1945) Campbell and Harlow	12 rhesus	BFL[1]	DR[2]	impairment[3]
(1948) Blum	2 chimps	BFL	DR	no change
(1936) Jacobsen	3 monkeys	UFA[4] then BFA	DR	no change impairment
(1951) Meyer, Harlow, and Settlege	12 rhesus	UFA or BFL	DR DR	no change impairment
(1952) Pribram, Rosvold, Kaplan	32 baboons	DLFA[5] VMFA[6]	DR DR	impairment[2] no change
(1952) Blum	6 rhesus	BFL DFA MLFA[7] VLFA[9]	DR DR DR DR	impairment impairment extreme impairment[8] no change
(1957) Mishkin	10 rhesus	VFA IFA[11] MLFA SFA[12]	DA[10] DA DA DA	no change impairment extreme impairment[8] impairment
(1954) Chow	7 rhesus	PULV[13] MD[14] PULV	DR DR	no change no change

SUMMARY Cont'd.

AUTHORS	ANIMALS	SURGERY	TESTS	RESULTS
(1956) Peters, Rosvold, Mirskey	11 rhesus	MD	DA DR	no change no change
(1956) Rosvold, and Delgado	14 rhesus	CN[15]	DA	impairment

[1]Bilateral frontal lobotomy

[2]Delayed response

[3]There was later improvement in DR performance in two animals

[4]Unilateral frontal ablation

[5]Dorsal-frontal ablation or Dorsal-lateral frontal ablation

[6]Ventro-medial frontal ablation

[7]Midlateral frontal

[8]Sulcus Principalis described as critical focus for test abilities

[9]Ventral-frontal ablation or ventro-lateral frontal ablation

[10]Delayed alternation test

[11]Inferior-frontal ablation

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[12]Superior frontal ablation

[13]n. pulvinaris

[14]n. medialis dorsalis

[15]Caudate nucleus

Campbell and Harlow (1945) and Blum (1948) reported studies in which animals with bilateral frontal lobotomies were eventually able to solve delayed response. Two other papers concluded that bilateral damage is necessary to produce a delayed response deficit; unilateral damage to the frontal lobes produced no effect (Jacobsen, 1936, and Meyer, Harlow, and Settlege, 1951).

Several papers have been concerned with lesions which are subtotal and include various amounts of the frontal lobe cortex. Five investigators (Pribram, Rosvold, Kaplan, 1952, Blum, 1952, and Mishkin, 1957) have reported from experimental data that the frontal lobe cortex in the area of sulcus principalis is a focal cortical area for delayed response abilities. It should be emphasized that a major group of investigators working with the delayed response test in monkeys have concluded that the critical foci for delayed response ability are in the midlateral frontal cortex, along the sulcus principalis. This conclusion has also implied that delayed response ability is a cortical affair. (These same workers point to the negative results in studies of thalamic nuclei as further evidence that subcortical centers are of little importance in delayed response).

The work of Rosvold and Delgado (1956) cast doubt upon these conclusions. Caudate nucleus lesions also produce delayed response deficit, in the absence of lesions in the

sulcus principalis. The fact that any surgery to the frontal lobes is likely to damage also the corpus striatum seems an important limiting factor to be accounted for in studies where frontal lesions have presumably been limited to the cortex.

Difficulty in the pre-response cue period as well as the conditions of stimulus presentation may be factors to account in part for the post-operative performance deficit. The post-operative animal may have difficulty in spanning the delay period in delayed response simply because he has not noticed the significant indicators for later correct response and therefore has nothing to remember during forced delay. The improved abilities of lesioned animals in testing conditions minimizing distraction and emphasizing distinctiveness of the cue have been evidence in this direction. Such drugs as Nembutal, Dial, and Insulin have also been reported as effective in restoring post-operative performance deficit. The mechanism of the drugs' action is obscure, but they may be effective through their action in allowing for a more complete response to cue. This action may occur through manipulation of the motivation level, as in insulin, or through control of hyperactivity and other post-operative behavior which interferes with appreciation of the pre-response cue.

As a final comment on the present literature, it should be noted that the paper of Chow and Hutt (1953)

provides an excellent review of behavioral testing in primates, with particular reference to delayed response work up to the date of the paper's publication.

CHAPTER II

GENERAL METHODS

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GENERAL METHODS

The present study has undertaken the study of caudate lesions in relation to delayed response deficit and has as its objective the gaining of information concerning the magnitude and locus of caudate injury necessary to produce delayed response deficit. An attempt is made to relate these findings to the other post-operative behavioral changes in an effort to throw light upon the underlying mechanism of the deficits experienced by the caudate lesioned animals of the test series.

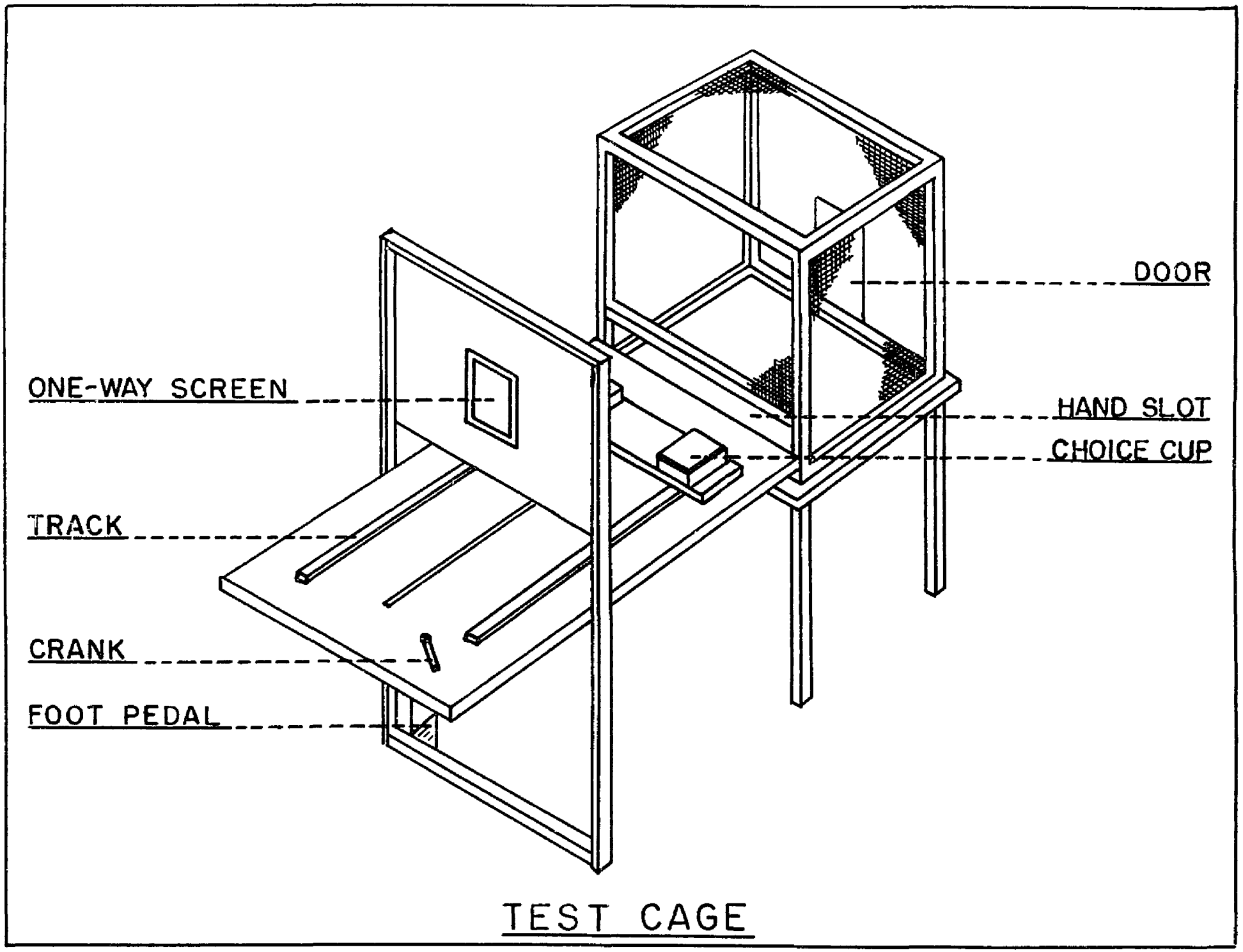
Description of the test apparatus and measuring techniques used follows:

CHAPTER II

GENERAL METHODS

I. PSYCHOLOGICAL TESTING

Cage Design and Modifications. The apparatus used in the behavioral training and testing of the animals in this study is a modification of the standard Wisconsin Apparatus. Figure I shows its basic construction. The animal is restrained within a wire mesh covered cage measuring three feet wide, three feet long, and three feet high. At the examiner's end of this cage, a slit two inches wide crosses the end of the cage horizontally, allowing the monkey to reach out and gain access to the choice boxes at the moment they are in contact with the cage front. At the level of the bottom of the opening in the face of the test cage, a piece of one-half inch plywood crosses the three foot width of the cage and extends back thirty-seven inches to the area where the examiner sits. Mounted on this platform is a dual track arrangement which allows a chain drive underneath to move a tray upon which are mounted the two choice boxes. Eighteen inches from the cage, a masonite board is mounted perpendicularly to provide a visual barrier between the examiner and the test cage. In the center of the partition a one-way vision screen is mounted to allow observation of the animal. Beneath this screen, a velvet curtain is hung so that it may be raised and lowered by


DOOR
ONE-WAY SCREEN
HAND SLOT
CHOICE CUP
TRACK
CRANK
FOOT PEDAL

TEST CAGE

a foot pedal mounted on the floor. This arrangement allows for the passage of the food tray behind the screen whenever it is necessary to remove the choice cups from the animal's view.

CHOICE CUP DESIGN

The design of the choice cups differs from the standard Wisconsin Apparatus. Two boxes four inches wide and two and one-half inches high, are mounted, one at the right and one at the left end, on the movable tray. Each box has a hinged lid which extends one-half inch beyond the top edge of the box. The animals may reach into the box after first raising the hinged lid. The top surface of each lid is equipped with removable tin cue markers which may be painted or otherwise distinctively marked. This feature makes the apparatus adaptable to both discrimination and delayed response type problems, as the boxes may be made alike or different at will.

REWARD AND MOTIVATION CONTROL METHODS

Food level of the animals was controlled, since it determines in large part the motivation of the animals to test for food reward. A standard maintenance diet of fruit, monkey chow, and vegetables was established for all test animals, at a level approximately one-fourth less than given the non-test animals in the colony. Vitamin preparations were fed to all test animals. Upon refusal to

test, food given outside the test room was cut to one-half the usual amount, and, infrequently, the animals were fasted completely for as long as thirty-six hours prior to testing. Variation in food level was confined in large degree to the preoperative period because monkeys were removed from the test string if they did not run more than twenty trials per day without food deprivation. As the subjects learned the test situation (and their frustration decreased) the average number of voluntary trials per day increased. (Two trained animals of the series would run 50-100 runs per test day without food deprivation). It was possible through this technique to gain post-operative test trials which were taken at the same level of food intake as the preoperative ones. All animals were weighed at periodic intervals to insure that no loss of weight occurred during periods of testing.

Other motivational control methods were employed besides diet restriction. A given animal was tested with a selection of his "favorite" foods if he had shown a preference during prior testing sessions. After the first animal in the series, all testing was carried out in a semi-darkened room, with a single spot light focused on the cue area and the feeding position of the movable tray. A test room was used which had no outside windows. This test room was located facing an inner corridor where outside traffic was slight and distracting noise at a minimum. Steps were

taken to minimize distractions during all test procedures.

SUBJECTS

The five Macaca Mulatta monkeys used in this study included four males and one female. They were selected from the available animals in the colony because they were in good health and had indicated a relatively stable activity-level in the activity apparatus to be described later. A total of seven animals were introduced into the psychological learning series. Two animals were dropped from the study because one animal failed to learn the problems submitted to it and the other one refused to run more than a few trials per day. Two types of notes were taken throughout the testing program. One type of data concerned the correct and incorrect trials run each day. Also, notes on the general behavior of each animal were kept daily in order to gain impressions of the "personality" of each monkey before and after surgery. The investigator was responsible for the majority of the handling, transport, and feeding of the learning series monkeys in order to establish maximum rapport.

PSYCHOLOGICAL TESTS

Two test procedures were used with all five animal subjects. A simple color discrimination test was used as a control, to demonstrate that post-operative monkeys are still able to perform accurately on a previously learned

task. The second test was the delayed response. Delayed response was used to demonstrate a loss of test abilities which follows caudate lesions in the monkey. These tests will be described in more detail.

YELLOW-BLUE DISCRIMINATION TEST

The discrimination problem was a simple discrimination between blue and yellow. The subject was rewarded for approach to the yellow-marked choice cup, which was placed alternately on the right or left side. He therefore avoided the blue-marked cup. A successful trial was rewarded with suitable bits of food placed within the correct choice cup. The yellow lid cover was shifted from right to left, between trials, in a predetermined random order. Randomization of right and left trials was achieved by preparing data sheets in advance marked with equal numbers of right and left trials obtained from a random numbers table. Three different data sheets of one-hundred trials each were used and rotated in order to prevent learning of the trial sequence by the animals. Training was continued on the yellow-blue discrimination problem until the animals made at least fifty consecutive trials at 90% accuracy or better. This performance was taken as the criterion of satisfactory preoperative learning.

DELAYED RESPONSE TEST

The other test used was the delayed response test,

using the direct method. Delayed response was selected as the critical test in the study reported here because this test has repeatedly shown deterioration following frontal lesions. When this test was administered, the yellow and blue cue markers were removed from the apparatus, leaving the right and left choice cups identical in appearance. The monkey was trained to watch the examiner and to note in which cup the examiner concealed food. The tray containing the choice cups was then removed from the view of the animal (behind the vision screen) for the delay period. At the conclusion of the delay period, the tray containing the choice cups was advanced to the feeding position where the animal could once again view the two boxes and make his choice between them. The response was scored as correct if the animal opened the box containing the food, and incorrect if he opened the non-baited box. Following an incorrect response, the monkey was prevented from opening the opposite (correct) box and was required to wait until after the next cue presentation and delay period before responding again. Training started with zero delay where one choice cup was baited and the animal was allowed to respond immediately. When the monkey had mastered this task with 20 consecutive correct responses (or more) the timed delay interval was introduced. The choice boxes were hidden from the animal's view--behind the screen--during the timed delay period. The animals were trained to a delay of five

seconds after cue before responding. The criterion of mastery of five-second delayed response was reached when the individual animal had responded for at least fifty consecutive trials at ninety percent accuracy. When criterion had been reached at five-second delay, fifteen-second delayed response was introduced. The criterion for fifteen-second delayed response was reached when the animal had made fifty consecutive responses at ninety percent accuracy.

At the conclusion of this training, the animal had mastered all delay intervals of the delayed-response test through fifteen seconds delay. In most of the animals no formal training or criterion trials were made with ten seconds delay, even though ten second delayed response was included in retention testing after operation. Criterion level performance on the fifteen-second test was used to indicate satisfactory ability to perform the easier ten-second test. Upon the completion of criterion testing on the discrimination and delayed response tests, the subjects were ready for operation and post-operative testing.

SURGERY

All of the operations included in this study were performed by Dr. George D. Davis. With the exception of the one animal which received a frontal-cortical ablation, all operative procedures involved sub-cortical stereotaxic lesions in the head of the caudate nucleus. A Johnson

Stereotaxic instrument was used. The sub-cortical operations were all essentially equivalent. Material from the operative notes of these procedures will be quoted as descriptive of the techniques used.

Anaesthesia was customarily induced by Sodium Pentobarbital injected intraperitoneally in doses of 0.6 mg. per kilogram of body weight. On occasion, slight additional doses were required to produce anaesthesia of sufficient depth for operation.

The monkey's head was shaved and cleaned with soap and water followed by saturation of the scalp with 70% alcohol solution. The anaesthesized animal was then placed in the prone position upon the stereotaxic instrument. In some cases, the animal's head was too large for perfectly aligned placement in the stereotaxic instrument. A correction was applied to the stereotaxic lesion coordinates used in these animals.

A unilateral stereotaxic operation will be described. The two stage caudate operations were similar, but repeated the same procedure two times.

A one inch saggital incision was made on the appropriate side of the scalp, with careful attention to hemostasis. Hemostats and surgical packs were used to control bleeding. A finder electrode was then attached to the stereotaxic apparatus and used to locate the proper location for a burrhole. Next, the skull was trephined,

exposing the dura. Bleeding and fluid ooze was controlled with packs and bone wax. The burrhole was then enlarged, exposing dura over the area where the electrodes would be inserted. The dura was then carefully incised. Electrocautery was employed to occlude bleeding blood vessels.

The next surgical step involved the placement of an average of seven stereotaxic lesions in the head of the caudate nucleus. The coordinate brain maps of Magoun[1] were used to determine electrode placements. Each small lesion was made with a monopolar electrode using three milliamperes of current for a duration of 45 seconds. A one minute interval was used between separate lesions to allow the electrode to cool. After the completion of the planned lesion series, the stereotaxic electrode was removed from the animal's brain and the galea was approximated with interrupted silk sutures. The scalp was then closed in similar fashion. Finally, one c.c. of Combiotic (R) was administered as a prophylaxis against post-operative infection.

The cortical operation used a different technique than the sub-cortical ones. For this operation, the animal was prepared and placed in the stereotaxic apparatus in the usual manner.

Next, a complete skin flap was outlined beginning

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[1] Personal communication.

anterior to the right ear and ending posterior to the right ear. A skull flap was reflected and the electro-surgical instrument was used to section the left temporalis muscle. Five burrholes were trephined: one on each side anteriorly, one on each side posteriorly, and one in the center of the left incision of the temporalis muscle. A Gigli saw was used to cut between the three burrholes on the left side, then the posterior transaggital cut was made, and finally the anterior transaggital cut completed the procedure. The dura adherent to the skull flap was freed, and the entire flap was hinged on the center of the right temporalis muscle. The dura covering the left frontal lobe was incised, with careful attention to hemostasis. Cortex was removed from the regions of the arcuate and principalis sulci by suction. This region was then packed and the procedure was repeated on the contralateral side. The surgical packs were removed and the dura was approximated with interrupted silk sutures. The bone flap was replaced and secured with interrupted sutures placed in the left temporalis muscle. The galea was approximated to further anchor the bone flap and subcuticular stitching accomplished final closure.

Post-operative care was the same for all five animals. The monkeys were fed full diet for at least a week following operation. During this time, they were observed carefully for signs of difficult recovery. In all cases

psychological testing was resumed as soon as the animal chose to work following daily exposures to the test situation. One monkey in the series (LS-7) tested on the day following operation. All animals were testing by the third post-operative day. This fact is considered to be a sign of minimal post-operative shock following lesioning.

POST-OPERATIVE DRUG TESTING

The five monkeys were tested for retention of delayed response and color discrimination following surgery. This testing was done to measure differences in the level of test performance after lesioning. When a sufficient number of post-operative retention trials had been made to establish stable and consistent results, the monkeys were tested for fifteen-second delayed response performance while under the influence of certain drugs. It will be remembered from the prior literature that Wade (1947) and Pribram (1950) have reported improvement in delayed response performance when frontal lesioned monkeys were tested under the influence of certain classes of drugs which have either depressant or excitant effects upon the central nervous system. However, certain technical difficulties have accompanied such experiments. One of the side effects of these drugs has often been to reduce the effective test motivation of the subjects. Drug treatment was sometimes followed by a reduction in the number of

trials made, and sometimes the animals refused all attempts to make them respond. Benzedrine, for example, is known for its depressant effects on the hunger drive. It is not surprising that monkeys often refused to test while under its influence, since the reward for test response was always food. Sedatives, such as Nembutal or Dial, operate to slow the animal generally. This phenomenon may result in indifference to the outside environment and indifference towards the specific test situation. Chance-level performance or complete refusal to test may easily result when sedatives are given in large dosages.

These adverse side effects were avoided as much as possible (in the selection of the drugs used in the present study). Drugs were selected which were known to be effective against the hyperactive syndrome found in caudate-lesioned monkeys. Drugs which have no untoward effect on hunger drive were selected in the hope that a high motivation to test might be maintained when the animal was testing under their influence.

Two main classes of drugs were used. The first drug, methyl-phenidylate (trade name Ritalin) is said to be a central nervous system excitant. This particular substance has found rather widespread use in the treatment of psychiatric disorders where a "psychic energizer" is of value. One of the paradoxical effects of this drug is to quiet the hyperkinetic caudate-lesioned monkey. In the present

experiment, Ritalin was administered by subcutaneous injection ten minutes before the subject was to be tested. Ritalin has been found to be effective in the hyperactive monkey within ten minutes after injection and it was hoped that effects on psychological test performance could be observed just as quickly. On the day following Ritalin treatment, sterile water was injected as a control technique, and test performance was noted in the same manner as when the animal was under Ritalin influence.

Since the effect of Ritalin on test performance is very rapid, it was possible to experiment with different amounts of the drug. Useful dose levels ranged from 0.25 mg. to 0.75 mg. per kilogram of body weight. The most generally effective dose for psychological testing purposes seemed to be 0.5 mg. per kilogram of body weight. However, smaller doses than this were effective in improving post-operative test performance (0.25 mg./kg. body weight).

Another drug, a central nervous system depressant, was used. Reserpine was injected subcutaneously for three consecutive daily doses in the dosage found to be effective in reducing hyperkinesia (0.25 mg./kg. body weight). Performance on fifteen-second delayed response was recorded three hours after the first reserpine treatment and once on each of the two succeeding treatment days. Progressive sedation of the monkey occurred during this three day period, and the monkey was usually very lethargic and

"tranquilized" by the third treatment day. Following reserpine treatment, fifteen-second delayed response was recorded in the same manner with a control injection of sterile water.

One other "ataraxic" drug was used. Meprobamate (trade name Miltown) has received widespread notice in the psychiatric literature as a drug which calms the subject without undesirable side effects. Meprobamate proved ineffective in controlling the post-operative hyperkinesis. It was also ineffective in producing any change in psychological test performance. Doses of 100 mg./kg. body weight produced nothing but a sore leg in the test subjects. Smaller doses were likewise ineffective.

A final drug, Benzedrine (amphetamine sulfate), was used in one caudate lesioned monkey. Amphetamine lowered test motivation and psychological tests made under these conditions were unstable and difficult to interpret. Testing with Amphetamine was not continued because it was in general an unsatisfactory drug when testing with food reward.

OTHER TESTING TECHNIQUES

I. Activity Testing

Random activity was measured at periodic intervals for all five monkeys. The apparatus used to measure activity has been described by Davis (1957). Two types of activity data were taken in the present study. The first involved

spontaneous activity of the isolated monkey for a two hour period. Activity measurements were gained through the use of an apparatus which isolated the monkey in a cage equipped with photoelectric counting circuits. Cage crossings on the bottom of the cage and also activity on horizontal bars at the top of the cage were measured. Summation of these measurements indicated total cage crossings per hour and also allowed computation of the monkey's activity on the right, left, top, and bottom of the activity cage.

A second activity apparatus measured spontaneous activity on a twenty-four hour basis. The activity cage used for the twenty-four hour studies was similar to the one previously described, except that it was completely enclosed and wired to provide light corresponding to sunlight during daylight hours. The cage was totally dark for a period of simulated night. Food was provided as usual and activity was measured for each hour over a twenty-four hour period. The advantage of this apparatus over the first simpler one is that it allows calculation of activity changes from hour to hour during the test period. "Activity patterns" for night and day may be determined.

Preoperative and post-operative activity measurements were compared. Activity changes through time were determined. These findings were related to behavioral test performance whenever possible.

II. Electroencephalography

Electroencephalograms were obtained[1] on several animals in the series before and after surgery when possible. An attempt was made to identify changes in the electrical activity of the brain following experimental lesioning. The results of these recordings will be covered in later discussion.

III. Neurological examination

Each of the subjects was examined neurologically before each operation and just before sacrifice. No abnormalities in muscular activity or sensory response were detected at any time in the experimental animals.

IV. Histological examination

Following completion of the entire testing program, the monkeys were sacrificed and their brains were subjected to the histological examination which is described in Chapter V.

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[1]These were taken by Dr. Henry Higman as a part of a larger series of electroencephalographic studies on animals with basal ganglia lesions.

CHAPTER III

RESULTS

BEHAVIORAL CHANGES FOLLOWING VARIOUS LESIONS

CHAPTER III

RESULTS

Since this chapter will report the results gathered from five different monkeys, following seven separate surgical procedures, the reader will be immediately curious about the selection of these lesions. For this reason the discussion of results opens with a resume which shows how the outcome of one operation led logically to the choice of each following operation.

A. RATIONALE OF LESION SELECTION

The surgery planned for the five monkeys which completed the testing training was selected to afford the maximum amount of behavioral information from a limited number of subjects. A rough outline of the prospective surgery was prepared prior to the study, but this plan was subjected to revision as data from the first operated animals in the series was completed. Figure 2 shows the operative procedures for the entire group of five monkeys, as well as a description of the test behavior changes occurring after the lesions were made. Tables I and II summarize psychological test data shown in Figures 3 - 7.

Since the object of the present experiment is to study the effects of lesions in the caudate nuclei on delayed response performance, the first monkey (LS-2) received bilateral stereotaxic caudate lesions. As expected, there was a complete loss of delayed response ability following these lesions. Performance on the discrimination test was not impaired, indicating a specific loss of test abilities, rather than a generalized decay of all previously learned habits.

The second animal in the series (LS-3) was designed to serve as an operative control subject. Figure 2 shows that this animal received bilateral, midlateral cortical lesions of the frontal lobes in the area of sulcus principalis. It will be recalled from Chapter I that Pribram

FIGURE 2

DIAGRAM OF THE LESIONS EMPLOYED IN THE EXPERIMENTAL SERIES

I. ANIMAL LS-2
"Tommy"

BILATERAL CAUDATE LESIONS ——— TOTAL LOSS OF DELAYED RESPONSE

II. ANIMAL LS-3
"Delores"

BILATERAL FRONTAL CORTEX LESIONS (Operative Control) ——— NO TEST LOSS

III. ANIMAL LS-4
"Antigone"

LEFT CAUDATE LESIONS ——— PARTIAL LOSS OF DELAYED RESPONSE

RIGHT CAUDATE LESIONS (Operation II) ——— TOTAL LOSS OF DELAYED RESPONSE

IV. ANIMAL LS-6
"Harry"

RIGHT CAUDATE LESIONS ——— PARTIAL LOSS OF DELAYED RESPONSE

V. ANIMAL LS-7
"Roscoe"

LEFT CAUDATE LESIONS (Operation I) ——— PARTIAL LOSS OF DELAYED RESPONSE

LEFT CAUDATE LESIONS (Operation II) ——— PARTIAL LOSS OF DELAYED RESPONSE

et. al. (1952), Blum (1952), and Mishkin (1957) have all concluded that the "foci" for delayed response abilities are in the frontal lobe cortex, in the area of sulcus principalis. Animal LS-3 of the present study had lesions confined to the frontal cortex about this "focal" area. LS-3 suffered no significant loss in test abilities following this operation, on either the discrimination or delayed response tests. This operation serves, therefore, as an operative control procedure which left the animal with no loss of test function but which included the greatest area of frontal cortical damage produced in the present series of experimental lesions.

The third monkey (LS-4) was the second animal to receive sub-cortical stereotaxic lesions. LS-4 was utilized to study the effects of bilateral vs. unilateral caudate lesions. Animal LS-4 was treated in such a way that the question of laterality of lesions could be investigated for caudate lesions. Operations in LS-4 were divided into two stages which could be compared with one another, as well as with preoperative test performance. The first set of lesions in LS-4 were in the head of the left caudate nucleus. This operation was followed (Figure 2) by a well defined partial loss of delayed response abilities. The second operation (LS-4) repeated the first operation on the contralateral side (right caudate head). After the latter operation, the bilateral ablation of the caudate nuclei

resulted in total impairment of delayed response. Discrimination test performance remained at criterion levels through both operative periods, demonstrating again the selective loss of test abilities found in monkey LS-2.

The fourth monkey (LS-6) was planned to duplicate the findings in the third animal. The first lesions in LS-6 were in the right caudate nucleus. This operation was followed by a partial loss of delayed response performance (comparable to the results after the first operation in LS-5). Monkeys LS-4 and LS-6 considered together demonstrate that laterality of caudate lesions makes no difference in test performance, regardless of the handedness of the animal. LS-6 died as the result of an accident before a second similar operation to the contralateral caudate head could be accomplished. This resulted in the premature termination of the experiment at this point.

The last monkey in the series, LS-7, was used to investigate whether a unilateral caudate ablation could be effective in producing a total loss of delayed response performance. Damage to the left caudate head was done first. A partial loss of delayed response abilities followed this operation, while discrimination test performance was not impaired. The second operation had as its aim the production of a second equal sized lesion site in the left caudate. It was hoped that LS-7 would show unilateral caudate damage after the second operation which was equal

TABLE I

NUMBER OF TRIALS AND ERRORS WITH PERCENTAGE CORRECT DEMONSTRATED BY FIVE MONKEYS PERFORMING THE YELLOW-BLUE DISCRIMINATION PROBLEM BEFORE AND AFTER OPERATION

Subject Number	Preoperative Control			Post-operative I Retention			Post-operative II Retention		
	No. of Trials	Errors	% Correct	No. of Trials	Errors	% Correct	No. of Trials	Errors	% Correct
LS-2	110	9	92	120	4	97	--	--	--
LS-3	233	19	92	31	0	100	--	--	--
LS-4	133	9	93	79	5	93	80	0	100
LS-6	60	5	92	118	9	92	--	--	--
LS-7	80	4	95	99	6	94	140	7	95

TABLE II

NUMBER OF TRIALS AND ERRORS WITH PERCENTAGE CORRECT DEMONSTRATED BY FIVE MONKEYS PERFORMING THE DELAYED RESPONSE PROBLEM BEFORE AND AFTER OPERATION

	Period of delay, (seconds)											
	0 Sec.			5 Sec.			10 Sec.			15 Sec.		
Subject Number	No. of Trials	Errors	% Correct	No. of Trials	Errors	% Correct	No. of Trials	Errors	% Correct	No. of Trials	Errors	% Correct
LS-2 (Pre-op)	40	2	95	67	5	92	--	--	--	50	1	98
LS-2 (Post-op I)	132	70	47	120	66	45	120	62	48	224	108	52
LS-3 (Pre-op)	148	23	84	125	6	95	--	--	--	218	8	96
LS-3 (Post-op I)	--	--	--	63	7	89	50	6	88	146	15	90
LS-4 (Pre-op)	54	3	94	80	7	91	--	--	--	78	2	97
LS-4 (Post-op I)	9	2	77	200	35	83	130	40	69	218	80	63
LS-4 (Post-op II)	243	81	67	200	86	57	87	40	54	137	62	54
LS-6 (Pre-op)	82	6	92	61	3	95	30	1	97	77	6	92
LS-6 (Post-op I)	73	4	94	284	81	72	148	51	66	254	118	53
LS-7 (Pre-op)	20	0	100	86	5	94	--	--	--	70	3	96
LS-7 (Post-op I)	80	11	86	247	33	87	90	49	45	237	122	48
LS-7 (Post-op II)	460	64	86	442	148	66	305	112	63	456	178	61

in the total amount of tissue damage to the bilateral lesions of the series. Delayed response abilities were further impaired by the final operation, but marked improvement in performance occurred with time. The implications of these findings are to be discussed in later chapters.

B. THE EFFECTS OF VARIOUS TYPES OF LESIONS ON PSYCHOLOGICAL TEST PERFORMANCE

The previous part of Chapter III has been devoted to a description of the test scores made by the five monkeys during the preoperative control and post-operative retention periods. This same data will now be discussed in terms of the effects of various lesions on test performance. The five bar graphs, Figures 3-7, show cumulative average scores on the discrimination and the four different delayed response tests. Average performance is shown before operation and after each of the operations performed on an individual subject.

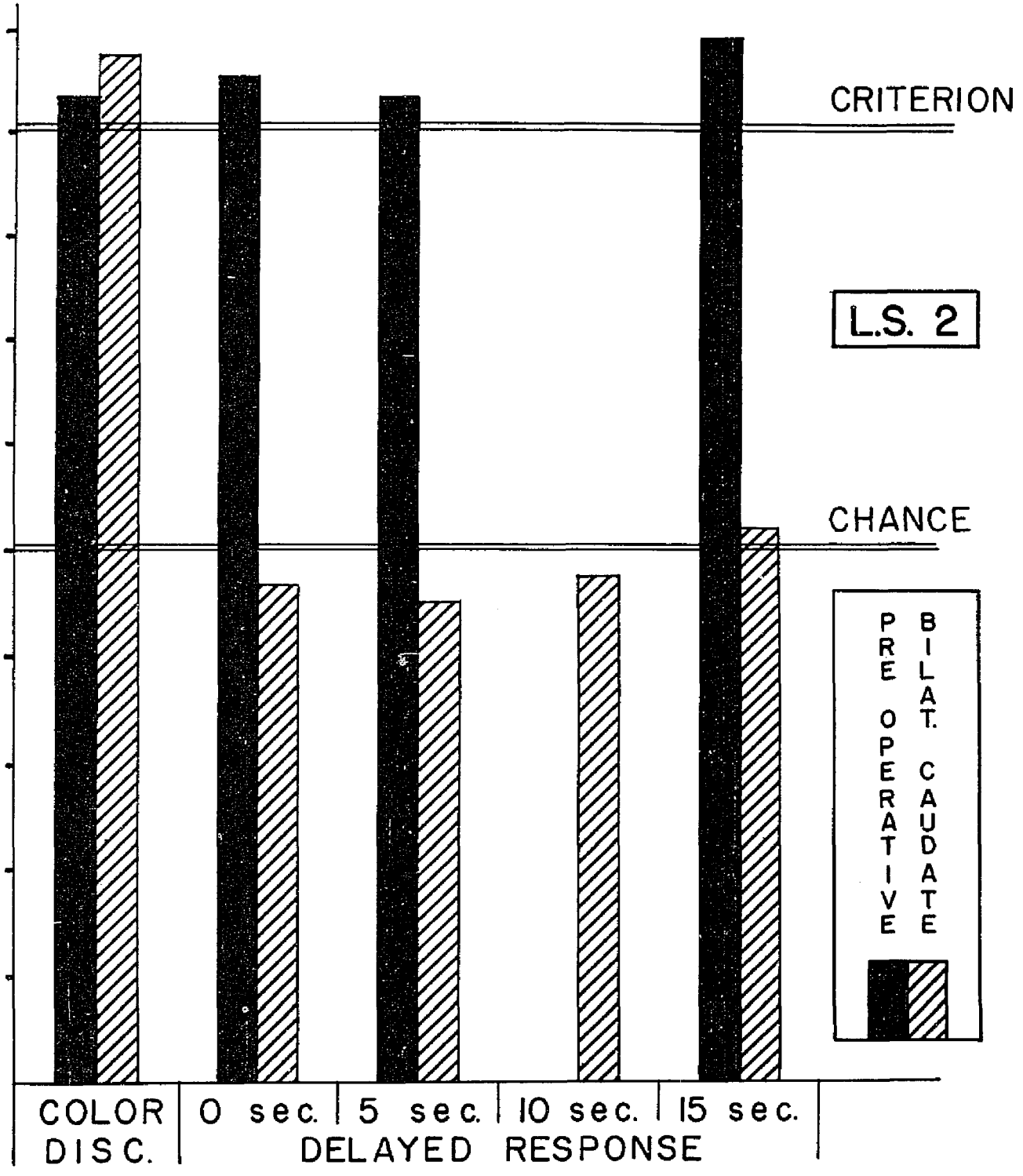
I. BILATERAL CAUDATE LESIONS

SIMULTANEOUS OPERATION

The first bar graph shown is for animal LS-2. This monkey received simultaneous bilateral lesions of the heads of both caudate nuclei. Figure 3 shows the effects of this operation on psychological test performance. The yellow-blue discrimination test was not affected; there was no

FIGURE 3

TEST AVERAGES AFTER SIMULTANEOUS BILATERAL CAUDATE LESIONS


CRITERION
L.S. 2
CHANCE
PRE OPERATIVE
BILAT. CAUDATE
COLOR DISC.
0 sec.
5 sec.
10 sec.
15 sec.
DELAYED RESPONSE

significant change in discrimination test scores after operation, except that LS-2 continued to improve in this test as a function of trials. The average discrimination score over preoperative trials of color discrimination was 92%, while this same average rose to 97% correct after operation.

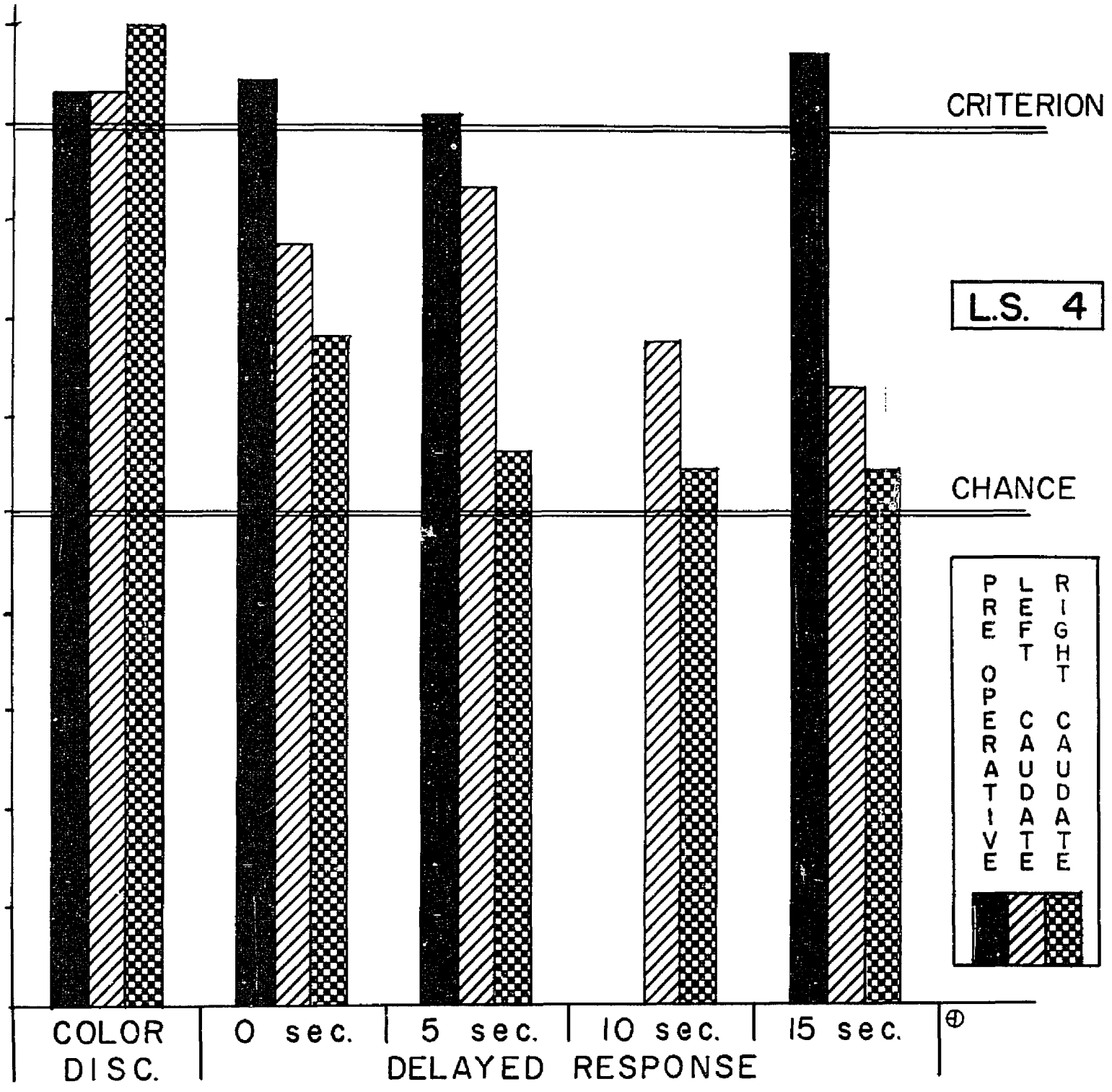
Delayed response performance, at all delay intervals, was completely lost following the simultaneous caudate lesions. The subject could do no better than chance performance when tested from day to day on zero, five, ten, and fifteen-second delayed response. LS-2 had performed at above 90% accuracy on all delayed response tests made before the operation. Certain drugs (to be discussed later) were effective in restoring delayed response abilities, but they had no long-term effect on test performance. There was no improvement in delayed response scores following lesioning. LS-2 continued to perform at chance accuracy levels throughout the post-operative test period.

SEQUENTIAL OPERATIONS

Figure 4 shows what happened to psychological test performance following a two-stage series of operations which produced first unilateral caudate damage and later bilateral damage. Animal LS-4 received lesions in the left caudate head in the first operation. Figure 4 shows that a partial loss of delayed response performance followed this operation. This loss was generally greatest for the

FIGURE 4

TEST AVERAGES AFTER SEQUENTIAL BILATERAL CAUDATE LESIONS


CRITERION
L.S. 4
CHANCE
PRE OPERATIVE
LEFT CAUDATE
RIGHT CAUDATE
COLOR DISC.
0 sec.
5 sec.
10 sec.
15 sec.
DELAYED RESPONSE

longest delay intervals (15 seconds) of the delayed response test and least for the shortest delay intervals (0 and 5 seconds). Although LS-4 scored below criterion accuracy on all delayed response tests made after the first operation, he scored 83% correct over 200 runs of five second delayed response, but only 69% correct at ten second delay and 63% correct at fifteen second delay. Discrimination test accuracy was unimpaired.

Following the lesions of the right caudate head, LS-4 scored only chance accuracy on all the timed delays of the delayed response test. LS-4 scored slightly better on zero delayed response (67% correct). This sequential series of caudate lesions duplicated the effects seen after a similar simultaneous lesioning. Delayed response was performed at chance accuracy, while discrimination test performance remained unimpaired. The sequentially lesioned animal (LS-4) seems to have been slightly more accurate in performing the zero interval delayed response task than the simultaneously lesioned monkey (LS-2). The cumulative percentage correct score (67%) made by LS-4 on zero delayed response following the second operation represents better than chance performance. However impairment was still very severe and did not change over the post-operative testing period. LS-4 was unable to span even the shortest period of delay (5 seconds) with correct delayed responses after both caudate nuclei had been damaged.

II. UNILATERAL CAUDATE LESIONS

RIGHT CAUDATE LESIONS

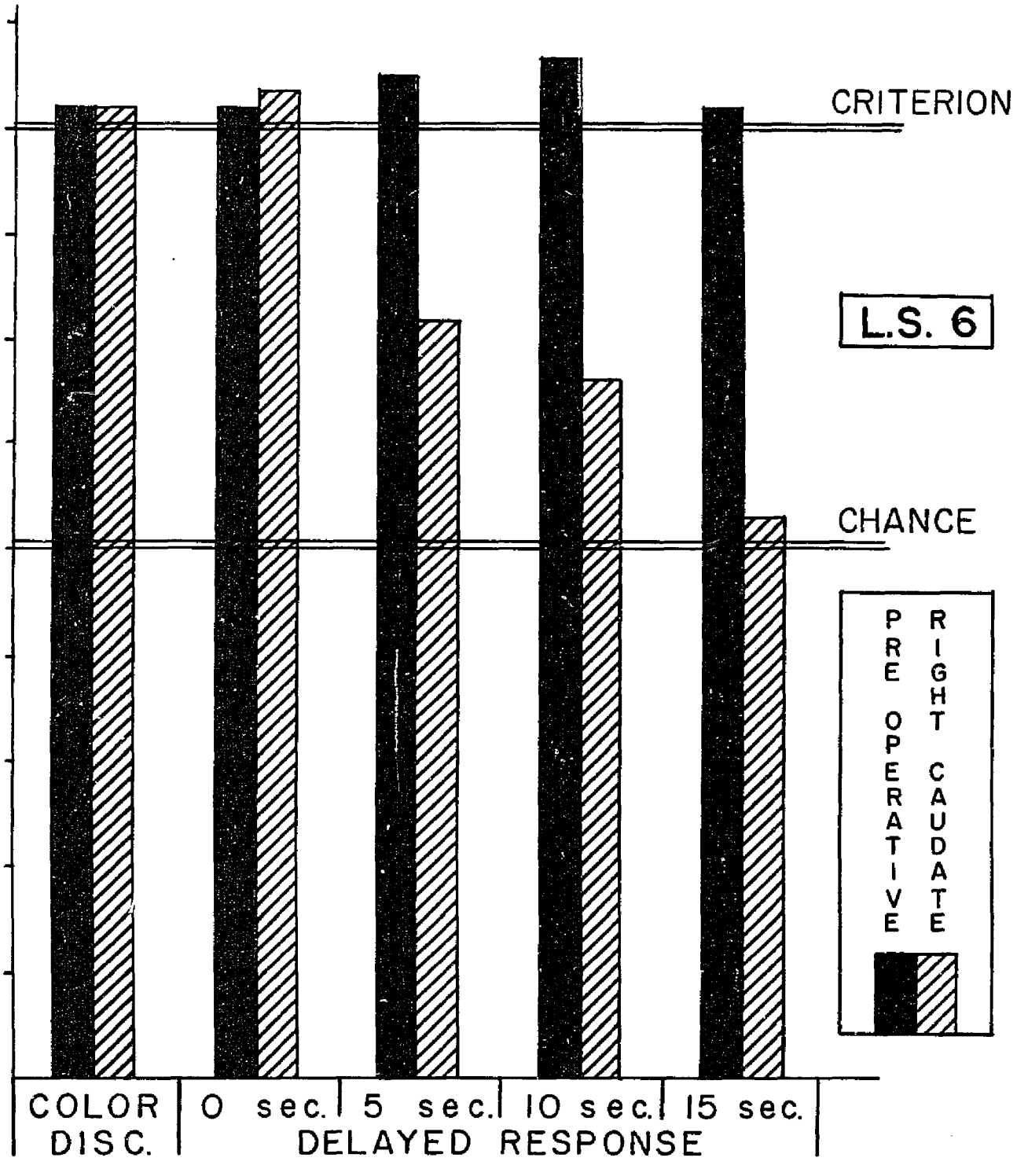
Figure 5 shows the average test performance of animal LS-6 which received a single set of lesions in the right caudate head. Although the accidental death of this animal prevented a second operation on the contralateral side, the data obtained from animal LS-6 shows test performance following a unilateral ablation of the caudate nucleus. Comparison of Figures 4 and 5 indicates that a partial loss of delayed response abilities followed unilateral caudate lesioning in both animals. Discrimination test scores were not affected by operation.

LS-6 achieved criterion level scores (95%) on zero delayed response after damage to the right caudate. LS-6 could not span a delay period with complete accuracy. Average accuracy dropped to 72% on five-second delayed responses. Impairment of performance was greater at ten seconds delay, where the average score was 66% correct. Fifteen-second delayed response performance was totally lost (53% correct).

Both the test subjects with unilateral caudate lesions (LS-4, LS-6) showed a loss of delayed response ability which was related to the delay interval. As the interval of delay became longer, the impairment of test accuracy was greater. Both subjects were unable to perform delayed responses after fifteen seconds delay.

FIGURE 5

TEST AVERAGES AFTER UNILATERAL CAUDATE LESIONS


CRITERION
L.S. 6
CHANCE
PRE OPERATIVE
RIGHT CAUDATE
COLOR DISC.
0 sec.
5 sec.
10 sec.
15 sec.
DELAYED RESPONSE

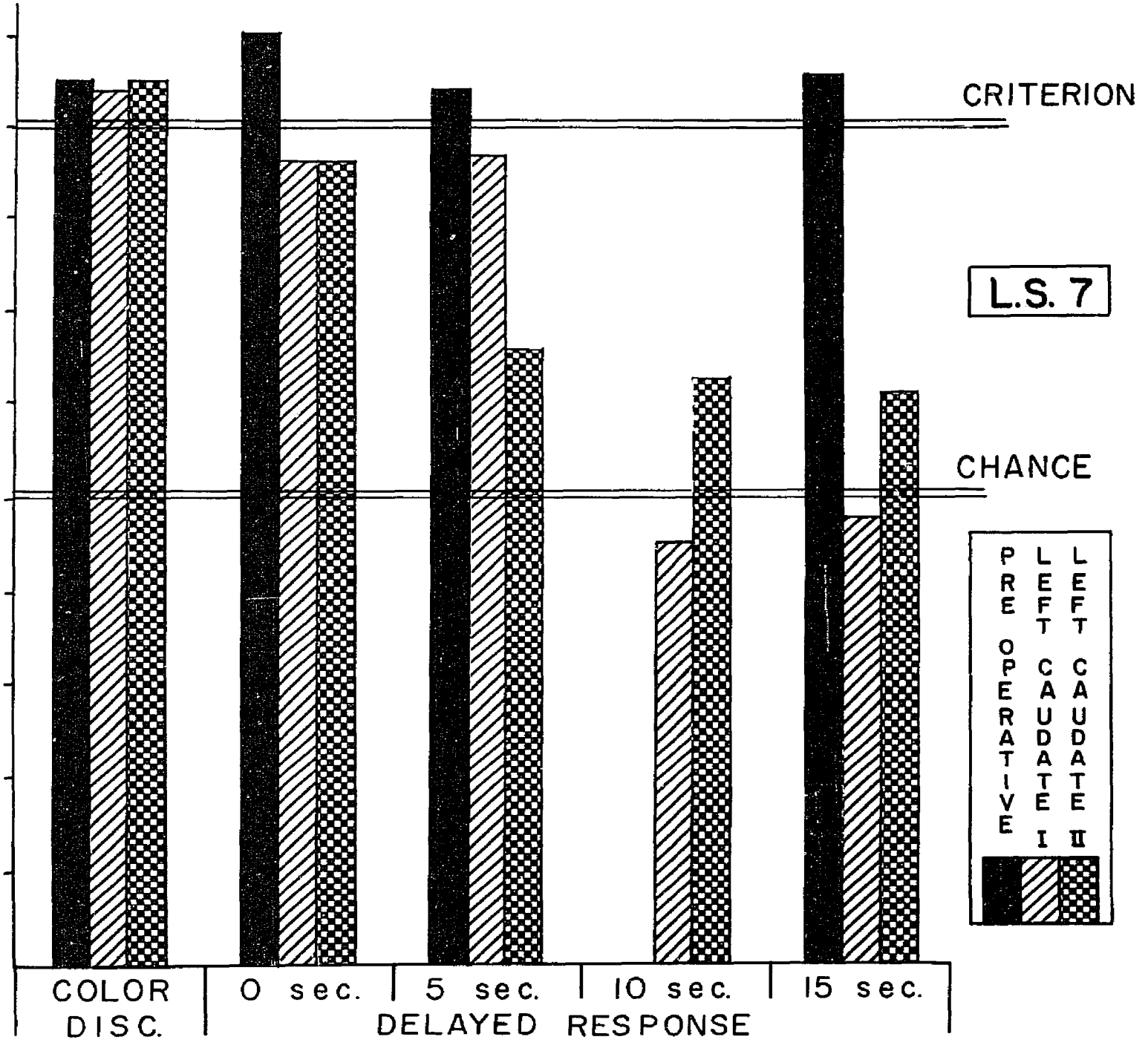
SEQUENTIAL LEFT CAUDATE LESIONS

Figure 6 shows the average test performance of animal LS-7, which received two sets of lesions of the left caudate nucleus. The results after the first caudate operation duplicated the partial loss of delayed response abilities seen in animals LS-4 and LS-6. LS-7 (after the first operation) was relatively unimpaired in his ability to perform delayed responses at short delay intervals. The average score was 86% on zero delay and 87% on five-second delayed response. LS-7 was unable to perform the delayed response accurately at delay intervals exceeding five seconds. Chance scores (45% correct) were made at ten seconds delay. Similar results were seen at fifteen seconds delay where the average score was 48% correct. Discrimination test performance was not impaired.

The test performance was very erratic following the second left caudate lesions in animal LS-7. Immediately after operation, delayed response performance was at chance levels on all four delay intervals (0, 5, 10, and 15 seconds). After the second post-operative week test performance began to fluctuate. LS-7 achieved scores of above 90% accuracy on several individual test days when the fifteen-and ten-second delayed response tests were given. Delayed response performance became completely unpredictable by the fourth post-operative week. The animal would score criterion accuracy on a given delayed response test

FIGURE 6

TEST AVERAGES AFTER SEQUENTIAL UNILATERAL CAUDATE LESIONS


CRITERION
L.S. 7
CHANCE
PRE OPERATIVE
LEFT CAUDATE I
LEFT CAUDATE II
COLOR DISC.
0 sec.
5 sec.
10 sec.
15 sec.
DELAYED RESPONSE

given on a certain day and then score chance level the next day. The effect of this erratic fluctuation in test scores was to progressively elevate the average accuracy scores on the five, ten, and fifteen-second tests. LS-7 ran at near criterion accuracy on zero delayed response rests made during the last ten days of the post-operative test period.

Two different testing techniques were used to show an interesting fact about this animal's test performance. It was found that test scores were maintained relatively stable when the animal ran only a few trials of a given delayed response interval. Tests of ten trials each of the four delayed response tests made in the last post-operative week resulted in frequent criterion level accuracy scores. Massed-trial testing of delayed response at a single delay interval was introduced because of this fact. Accuracy scores were computed for massed trials given for a single test on a single day. The results indicated that LS-7 was able to maintain criteron accuracy over a hundred trials of zero interval delayed response made on one test day. A very different performance curve was generated with massed timed interval trials. Massed five second trials were made under the same conditions that governed the zero delay trials. Increasing the number of five-second trials run in a single day resulted in a rapid decrease in the accuracy of test performance. The first twenty five-second trials made on such a day were made at or near criterion accuracy.

Progressive decay in test accuracy occurred. LS-7 would make a hundred five-second test trials in a given test day; performance on the first fifty of these trials would be above chance, while performance on the last fifty would approach chance (50% correct). A similar finding was made when ten and fifteen-second tests were made under "massed trial" conditions. LS-7 could respond correctly to even the longest delay intervals of the delayed response test if the number of trials demanded of him was not too great. These findings were ascribed to very critical motivation levels in this animal. Motivation was high enough to allow the animal to perform the test for short periods of time but not high enough to sustain performance on the harder tests for extended numbers of trials. Before the operations, the normal LS-7 would run similar "massed trials" of long delays with sustained criterion accuracy. LS-7 did not show the elevation of random activity expected after caudate lesions. He had far more pre-response ability than was shown by any of the other caudate lesioned animals. Final evaluation of his performance was postponed until histological examination of the brain could be made. The possibility of a faulty operation could not be excluded while the animal was yet testing. The experiment was terminated when test performance was relatively stable over a single test week. Analysis of test performance was based on all of the trials made after the second operation

because there seemed to be no real experimental evidence for doing otherwise.

Figure 6 shows the cumulative averages of behavioral tests made following the second left caudate lesions. Animal LS-7 showed no further impairment in zero interval delayed response scores (accuracy 86%). Five-second test performance was further impaired following the second operation. The five-second average dropped to 66% correct. Performance on ten-second delayed response improved after the second lesions. Cumulative percentage correct was 63% compared to 45% correct scored after the first lesions. Fifteen-second delayed response performance also improved after the second operation. The average performance over the second post-operative trials was 61% compared to 48% correct over the first post-operative trials. The improvement in delayed response accuracy at ten and fifteen seconds delay was due to the scores made in the last few test weeks rather than being the effect of immediate improvement following the second set of lesions.

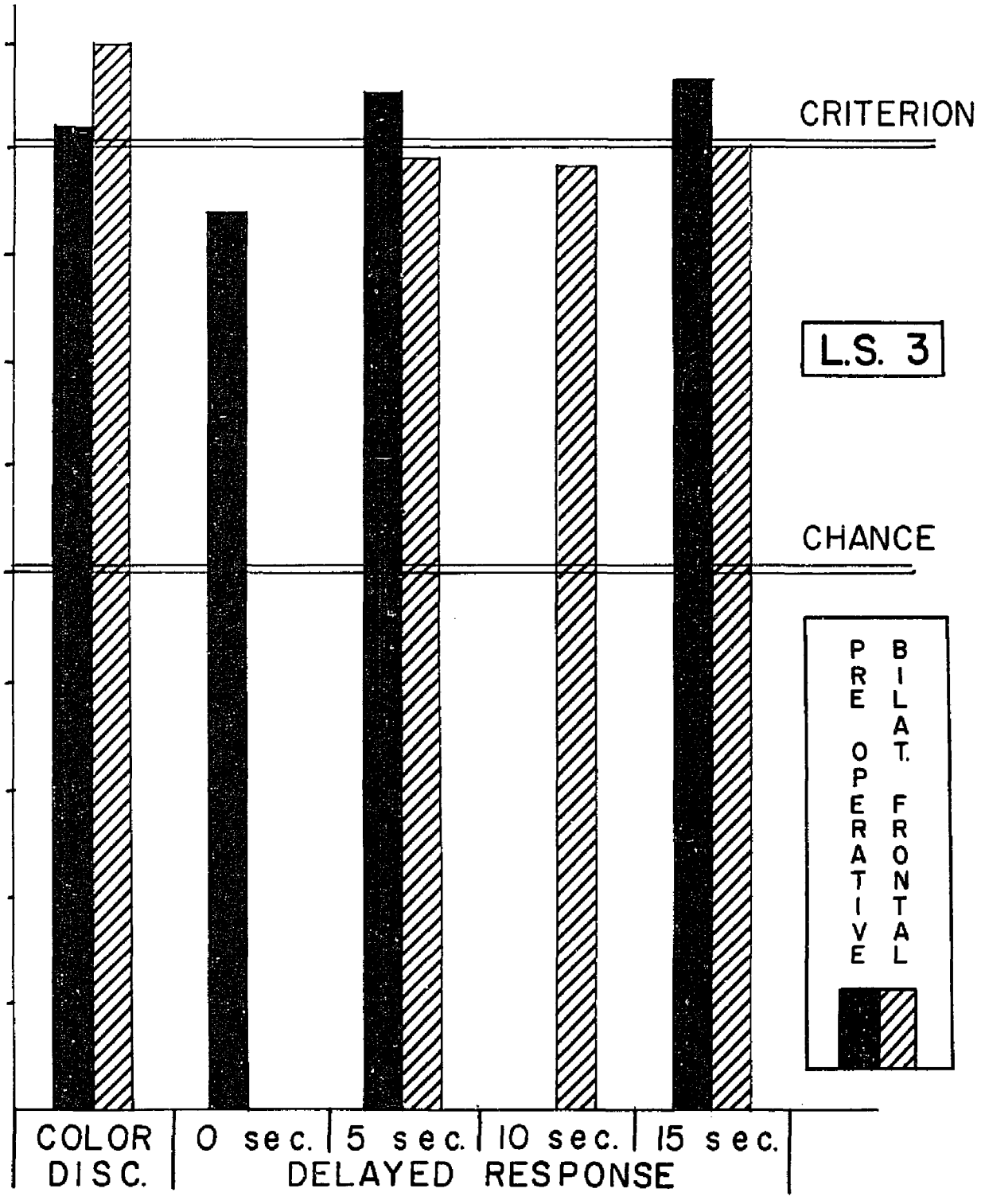
III. CORTICAL LESIONS

Figure 7 shows the average test performance of animal LS-3. This subject served as the operative control animal of the present series. LS-3 received midlateral frontal cortical lesions in the area of sulcus principalis. There was no significant change in test performance on either discrimination or delayed response tests following this

FIGURE 7

TEST AVERAGES AFTER BILATERAL

FRONTAL DECORTICATION


CRITERION
L.S. 3
CHANCE
PRE OPERATIVE
BILAT. FRONTAL
COLOR DISC.
0 sec.
5 sec.
10 sec.
15 sec.
DELAYED RESPONSE

operation. LS-3 scored a cumulative accuracy score of 90% on the fifteen second delayed response test. Five and ten second delayed response accuracy scores were 89% and 88% respectively.

Sub-cortical caudate lesions were the only ones which impaired delayed response test performance in the present experiment. Cortical ablation, even when it covers an area reported in the literature as critical for delayed response abilities, produced no effect.

SUMMARY

When all of the testing on the five experimental monkeys is considered, it is clear that comparatively small caudate lesions are followed by very large deficits in delayed response performance. The pattern of delayed response loss was highly consistent when animals with similar lesions were compared. Table III summarizes the test data for the various lesions by statistical significance. The findings of this part of the study may be summarized as follows:

1. Restricted bilateral caudate lesions are followed by a specific loss of learned abilities.
2. No loss in color discrimination test ability followed caudate lesions.
3. Unilateral lesions of the caudate result in partial loss of delayed response. This loss is severe at long periods of forced delay and moderate at shorter delays.

TABLE III

CHI-SQUARE VALUES FOR COMPARISONS OF PRE- AND POST-OPERATIVE PERFORMANCE OF SUBJECTS IN TWO LEARNING TESTS

LESIONS (SUBJECTS)		POST-OPERATIVE TESTS				
		DISC	DELAYED RESPONSE (Seconds)			
			0	5	10	15
CORTICAL LESIONS	(LS-3)	1.6	x	1.7	x	5.3
CAUDATE LESIONS						
UNILATERAL						
RIGHT	(LS-6)	0.0	0.0	13.9*	10.2*	36.1*
LEFT ONCE	(LS-4)	0.0	x	2.8	x	31.7*
LEFT ONCE	(LS-7)	0.0	1.8	2.9	x	47.9*
LEFT TWICE	(LS-7)	0.1	0.0	25.4*	x	30.9*
BILATERAL						
SIMULTANEOUS	(LS-2)	1.7	27.1*	39.8*	x	34.5*
SEQUENTIAL	(LS-4)	4.0	15.5*	18.7*	x	41.3*

*Significant at .01% confidence level (Chi-Square .01 = 6.6)

4. Laterality of lesions makes no difference, regardless of the subject's handedness.

C. QUALITATIVE CHANGES IN BEHAVIOR FOLLOWING VARIOUS LESIONS

This part of chapter III is devoted to a discussion of behavior changes noted during the daily behavioral testing sessions. These changes may be classified as qualitative ones. They were not directly measured as was psychological test accuracy. Qualitative changes following lesions are very important to the understanding of what has happened to the monkey to produce a selective loss of delayed response abilities.

I. CAUDATE LESIONS

1. Affective changes. The post-operative caudate lesioned monkey displays what might be called a flattening of emotional tone. The German term Witzelsucht (wit-sickness) has been used for this same emotional change when it occurs following frontal lobe ablation in monkeys and in man. Normal monkeys are very interested in the environment about them. They are always showing this interest by exploratory behavior and by visible reaction to external stimulation. This interest disappears after caudate operations. The animal no longer explores his surroundings. He seems too much involved with stereotyped motor activity to give much attention to what goes on about him.

Another consequence of this emotional flattening is

that such animals lack a normal range of emotional response to the environment. The monkey performs in a mechanical and stolid way. When it is in this state, the subject's tolerance for frustration increases. He shows no emotional response to repeated failure and loss of reward on the delayed response test. Such monkeys will test for extended periods of time getting only chance reward. This means that the animal is receiving food on only half of the test trials; normal monkeys would be expected to refuse testing after only a few such trials or to change their mode of attack on the problem in an attempt to better the reward. This is not the case in caudate lesioned monkeys. It should be recalled that the operated animal was once able to perform correctly on the delayed response test. Following operation, the animal regresses to a very simple test response hypothesis. This is usually a simple position habit (such as was seen when the normal untrained monkey was introduced to the delayed response problem for the first time). Thus, the lesioned monkey may respond for innumerable test trials by choosing always the right cup and never the left one. One would infer from watching these animals test that the animal is choosing the easiest possible way out of his dilemma. He shows no signs of caring what happens to him or whether he wins or loses in performing the test problem. Indifference pervades everything caudate lesioned monkeys do in the test room. The animal's test approach is erratic and unpredictable;

lesioned monkeys have been noted to open a correct goal box and not remove the food, even when they are hungry.

Post-operative test animals often seem to want to be left alone. Before operation, these same animals seemed to love their daily trip to the test room. "Game behavior" often resulted when the subjects manipulated the test apparatus with gusto and obvious enjoyment. Frustration was shown by tantrums and pouting when performance was poor. A profound change occurs after caudate operations. The monkeys are often suddenly difficult to handle and to remove from their living cages. They become sullen and uncooperative. They resist actively the attempts of the examiner to get them into the transport cage. It is interesting that the struggle just described usually ends when the animals are finally inserted into the transport cage. Then the animal gives up and seems to resign himself to his fate. Such animals have been left in the confined transport cage for periods of a half hour or more, and yet they seldom if ever attempt to escape.

Normal monkeys are very spontaneous creatures. They are always trying new ways to do things. Untrained animals shift from position to alternation test hypotheses. They may stand on one foot while testing or roost on the water fountain between trials. These non-effective modes of response are progressively eliminated when the animal arrives at insight which allows it to respond correctly to

the test problem. All of these changes occur in a dynamic and always changing creature whose variability is the rule rather than the exception. Caudate lesioned monkeys are no longer spontaneous. They react in the same way time after time. They have become unoriginal and seldom change their hypothesis about the test problem. They do not profit from experience; they seem to have no insight into their lack of success. Furthermore, they are not apparently unhappy about this state of affairs.

2. Drive level. Drive level, or the number of test trials run voluntarily per test day under standard conditions, was reduced immediately following operation in almost all animals. This effect was temporary in most of the subjects and may be related to somewhat lowered vitality due to post-operative shock. A permanent effect on drive level was seen in some animals. Although it was not necessary to restrict diet greatly to get the subjects to test, individual preferences for a particular food became more important after operation. This effect was seen when both the discrimination and delayed response tests were given. One caudate lesioned animal would work only for orange pieces (his favorite food), whereas the same animal would test for almost any food before the operation. Lesioned monkeys had little interest in the tests and had to be paid dearly for their efforts.

All of the test animals were able to perform the color discrimination problem at criterion accuracy following surgery. However, if visual distraction and/or noise were introduced into such a test series, criterion performance quickly fell to chance accuracy levels. A simple position habit might suddenly appear under such abnormal testing conditions. If the task became too difficult for the animal, he simply gave up. The effects of distraction were many times greater in the lesioned monkey than in the normal subject. Besides pointing to the importance of standardized test conditions, the effects of distractions on the lesioned monkey are felt to be related to the fact that the animal apparently has less motivation to perform any test. Reward is no longer of normal importance in regulating his behavior.

3. Changes in motor activity. Motor changes were very marked in some monkeys in the series. Caudate lesioned monkeys were in general very hyperkinetic. The pattern and amount of this activity was measured, and is discussed in chapter V.

Other motor changes which were noted included a grasping syndrome. The animal was noted to clinch and relax his hand in a rhythmical manner. A similar symptom was seen when the subjects slapped the bars of the test cage with alternate hands. This type of behavior was sometime seen (in the lesioned monkey) during the interval of delay in

the delayed response test.

Animals with caudate lesions often paced the test cage constantly. The monkey usually followed the same path in his to-and-fro pacing from day to day. The most active animals of the series underwent post-operative testing while pacing constantly in this way. This is interpreted as another sign of the stereotyped motor behavior seen in caudate lesioned monkeys.

4. Changes in response to cue. The normal monkey who has learned the delayed response problem shows a definite response to seeing food placed in one of the two cue cups (delayed response test). This pre-response behavior may consist of actual changes in posture or placement. The monkey may move to the side of the test cage nearest the baited cue box and maintain this position through the interval of forced delay. Other pre-response behavior is seen in movement of the head and eyes towards the baited cue box. Motor mechanisms such as slapping the correct side of the cage with the hand were also seen. As preoperative training progressed and the subject became more adept in the delayed response problem, each monkey developed a set of pre-responses which served to notify the examiner that he had reacted to the cue and would be able to respond correctly after the period of delay.

This pre-response behavior disappeared after caudate lesions and the animal regressed to the simpler responses

(position habits, alternation habits, etc.) which have already been discussed. No response was apparent at the time of delayed response cue, and the animal reacted with an incorrect response after the delay period. If one considers that the delayed response test consists of a series of temporally related responses which begin with pre-response to cue and end after the delay with the correct goal response, then caudate lesioned animals experience difficulty at the start of this series because they fail to make the necessary pre-response to external cue. There appear to be other factors which affect delayed response performance, however. The length of the delay period is one of these factors. Monkeys with unilateral caudate lesions are still able to make the pre-response when the cue is presented. They can also perform the delayed response if the delay is short enough. Animals with unilateral lesions fail in delayed response tests where the delay interval is much beyond ten seconds duration. Making the delay interval longer places greater hardships upon the subject. He must not only respond correctly to the cue but also maintain this response set over extended periods of delay. The failure of unilateral caudate animals at longer delays may be related to decreased interest in the test situation. When the test becomes too difficult, the lesioned animal is willing to give up and accept the lessened reward following chance level performance.

Unilateral caudate lesioned subjects were also unstable at times in the number of trials which they would run from day to day, although the accuracy of various test scores made on these days was stable. Observation of monkeys with unilateral caudate lesions suggests that motivation to test is sufficient to allow good performance if the pre-response behavior is rewarded quickly enough with the opportunity to feed (as in short delay intervals). If the subject is more or less immediately rewarded for his attention, then he goes ahead and completes the complex reaction chain. Delay of reward to longer periods of time finally reaches a point where test motivation is insufficient and the animal quits responding to the cue.

II. FRONTAL CORTEX LESIONS

The main qualitative effect of frontal cortical operation seems to be on test motivation. It will be recalled from the first section of the present chapter that all psychological test functions were preserved following frontal cortical lesions in animal LS-3 of the present study. The frontal lesioned monkey could respond accurately to the psychological tests, but it showed less inclination to test after operation. Reduction of outside feeding was effective in maintaining accurate test scores. Similar manipulation of diet had no effect on the accuracy of delayed response scores in the caudate lesioned monkeys.

The random activity of the frontal animal was somewhat increased in the test cage following surgery. However, pre-response behavior remained very satisfactory. The animal was capable of interrupting its pacing pattern to make a strong postural pre-response. This pre-response behavior was unlike anything seen in the caudate lesioned subjects. The fact that a highly active animal can still perform on the delayed response test is evidence that delayed response abilities are not dependent upon activity changes. Other evidence in this direction will be discussed in other chapters.

The frontal cortical lesioned monkey did not show the symptoms of flattened affect. There was little change in her behavioral patterns in the test room, except for generally increased activity.

CHAPTER IV

THE EFFECTS OF DRUGS ON ANIMAL BEHAVIOR FOLLOWING VARIOUS LESIONS

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Various dosages of several drugs were used in post-operative psychological testing with the monkeys who had received caudate surgery in this study. These were Methyl Phenedylate (Ritalin (R)), Reserpine (Serpasil (R)), Amphetamine (Benzedrine (R)), and Meprobamate (Miltown (R)).

A brief discussion of each drug in terms of what were found to be optimal dosages for restoring delayed response performance follows.

A. RATIONALE OF DRUG DOSAGES

Some interesting facts have come to light concerning the effects of varied dosage levels on behavioral test performance. Dosage level will be discussed for each drug used in the study.

I. RITALIN

Methyl Phenidylate, injected subcutaneously, has been shown to have an almost immediate quieting effect on post-operative hyper-activity. The same quick action has been observed in studying the effects of the drug on test performance.

The smallest Ritalin dosage which changed test performance was 0.25 mg. per kilogram of body weight. This small dosage produced total restoration of test function in some cases, and in other cases there was only a slight change in test accuracy.

The most frequently used Ritalin dosage was 0.5 mg. per kilogram body weight. This dose is also the minimum dose which has changed activity levels. This dosage was uniformly effective in restoring criterion level test performance, even in the most severely impaired animals. The behavioral changes accompanying Ritalin treatment were most often seen at this and greater doses, but they were sometimes seen when half this dose was given. Occasionally, animals were reluctant to test immediately following 0.5 mg./kg. Ritalin doses. In these cases,

attempts to test were made at five-minute intervals following the introduction of the subject into the test cage. Criterion level test performance resulted when the subject finally began to test.

Some Ritalin testing was attempted with dosages as great as 0.75 mg./kg. of body weight. Subjects were very reluctant to test immediately following doses of this magnitude. Immediate delayed response testing was usually refused and it was necessary to wait for periods of up to a hour before the monkey would accept the test. Behavioral changes were great under this dosage of the drug, and often seemed to interfere with attention to the test problem.

II. MEPROBAMATE

Since Miltown had no effect on either random activity or psychological test performance, the effects of varied dosage were not carefully studied. Intramuscular injections of 50 mg./kg. body weight were given twice before testing. The first injection was followed twelve hours later by a second equal one and then psychological testing was begun. No changes in test performance were noted.

The same lack of effect was seen during psychological testing which was preceded by two similarly spaced doses of 100 mg./kg. The conclusion was made from the data that no physiologically practical dosage of Miltown was likely to improve psychological test performance in the caudate

lesioned monkey.

III. SERPASIL

Reserpine did not effect test performance with the rapidity seen with Ritalin. For this reason, the effects of varied dosage levels were more difficult to study. Three equal doses of Serpasil were made at twenty-four hour intervals. Testing was not begun until at least three hours after injection. No significant change in test performance was usually experienced until after the second or third Serpasil treatment. Effective blood levels of reserpine were assumed to mount throughout the three day treatment period, but no actual measurement of this level was possible.

The most common dose of Serpasil used in the psychological test studies was 0.25 mg./kg. of body weight per day. This same dosage has been effective in reducing activity level in caudate lesioned animals. When smaller doses were tried, the effect on test performance was not clear cut. One test day was run, for example, at half the usual dose. Psychological test performance was above the post-operative average, but below the criterion level performance experienced with larger doses. Quarter milligram reserpine doses were used in all drug studies which were used in the recorded performance tables because this dose was uniformly effective in producing criterion level test performance.

The effect of successive Serpasil injections is a cumulative one on psychological test accuracy. In evaluating the effects of the drug on delayed response abilities one must consider not only the magnitude of an individual dose but also the number of such treatments which preceded the test session in question.

B. EFFECTS OF DRUGS ON POST-OPERATIVE TEST PERFORMANCE

In Table IV appear the data for post-operative fifteen second delayed response trials with and without drugs. Table V shows values of chi-square comparing post-operative performance on fifteen second delayed response with performance on the same test under the influence of four drugs. Figures 8-11 show average drug performance for each subject and lesion.

It is seen that at fifteen seconds delayed response phenidylate restores test performance to preoperative accuracy. This is true regardless of the type of caudate lesion (Table V). Examination of Figures 8-11 shows that the test effects of phenidylate are not permanent. Control injections of water on the day following phenidylate treatment resulted in fifteen second delayed response scores which were similar to the normal preoperative average.

Reserpine restored fifteen second test accuracy in two monkeys with bilateral lesions and in one monkey with unilateral lesions. These results were statistically

significant but temporary. Water injection trials were again no different in accuracy than other non-drug post-operative test trials.

Meprobamate had no effect on impaired test performance at fifteen seconds delay. Amphetamine had no significant effect in the one case where it was used.

Two different drugs have been shown to restore impaired delayed response accuracy. Reserpine does not seem quite so effective as phenidylate because phenidylate is effective much sooner after injection with very small doses, and the effect is uniformly greater on performance.

TABLE IV

THE INFLUENCE OF DRUGS UPON POST-OPERATIVE FIFTEEN SECOND DELAYED RESPONSE SCORES

SUBJECT-OPERATION	DRUG											
	PHENIDYLATE			MEPROBAMATE			RESERPINE			AMPHETAMINE		
	No. of Trials	Errors	% Correct	No. of Trials	Errors	% Correct	No. of Trials	Errors	% Correct	No. of Trials	Errors	% Correct
LS-2 (Post-op I)	143	16	88	50	22	56	17	2	88	--	--	--
LS-4 (Post-op I)	109	17	84	--	--	--	--	--	--	--	--	--
LS-4 (Post-op II)	39	3	92	21	9	52	19	1	95	66	24	63
LS-6 (Post-op I)	77	4	95	65	27	58	10	0	100	--	--	--
LS-7 (Post-op I)	100	4	96	--	--	--	35	2	94	--	--	--
LS-7 (Post-op II)	51	3	94	--	--	--	--	--	--	--	--	--

TABLE V

CHI-SQUARE BETWEEN FIFTEEN SECOND DELAYED RESPONSE PERFORMANCE OF CAUDATE LESIONED SUBJECTS POST-OPERATIVELY AND UNDER FOUR DRUGS

LESIONS (SUBJECTS)	FIFTEEN SECOND DELAYED RESPONSE			
	PHENIDYLATE	MEPROBAMATE	RESERPINE	AMPHETAMINE
CAUDATE LESIONS				
UNILATERAL				
RIGHT (LS-6)	41.5*	0.3	x	x
LEFT ONCE (LS-4)	14.5*	x	x	x
LEFT ONCE (LS-7)	65.7*	x	23.9*	x
LEFT TWICE (LS-7)	20.5*	x	x	x
BILATERAL				
SIMULTANEOUS (LS-2)	51.8*	0.1	7.1*	x
SEQUENTIAL (LS-4)	16.8*	0.0	9.5*	1.1

*Significant at .01% confidence level (Chi-Square .01 = 6.6)

FIGURE 8

EFFECTS OF DRUGS ON POST-OPERATIVE DELAYED RESPONSE SCORES, ANIMAL LS-2

P = Phenidylate

M = Meprobamate

W = Water

R = Reserpine

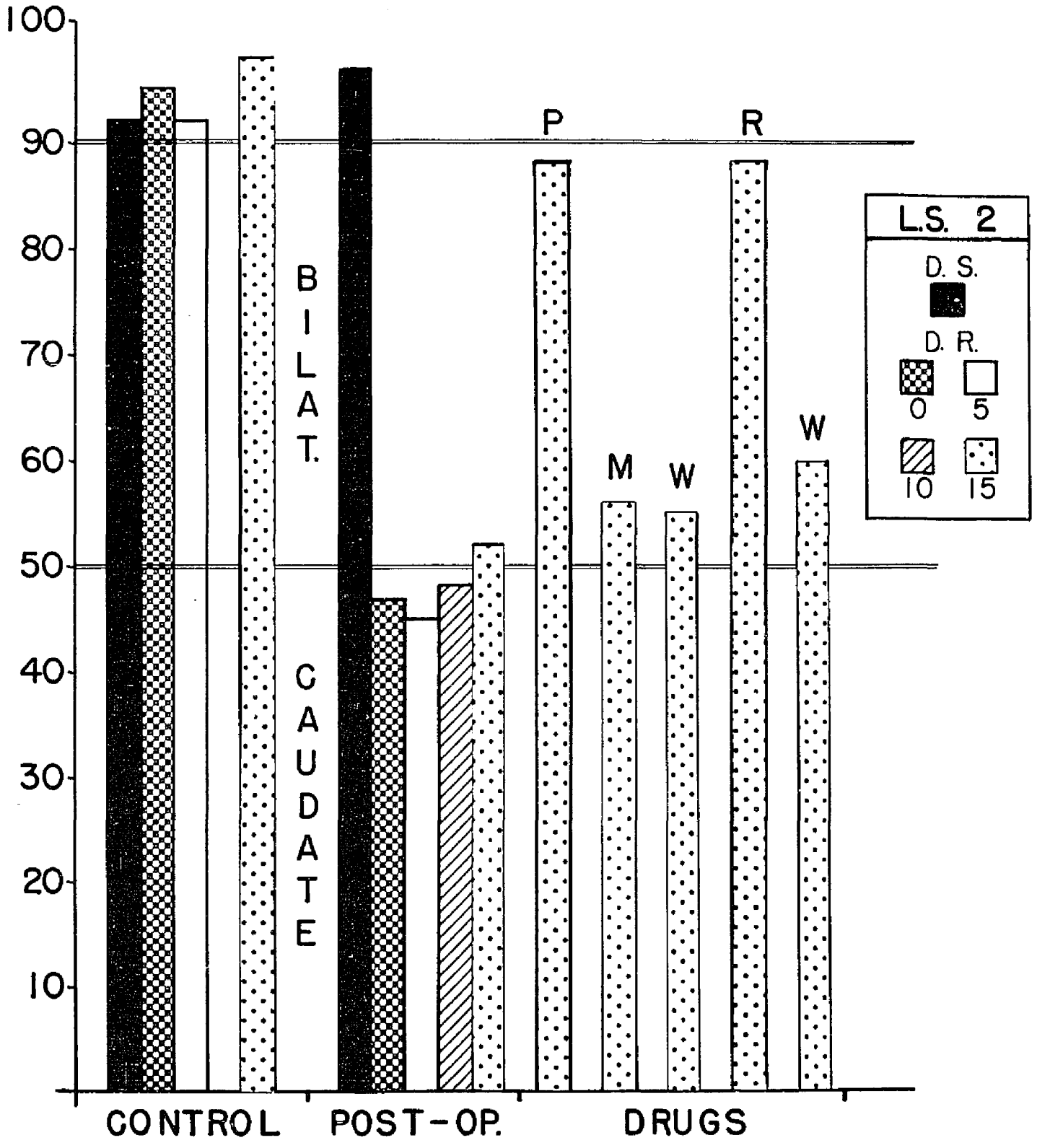

100
90
80
70
60
50
40
30
20
10
BILAT.
CAUDATE
P
R
M
W
W
L.S. 2
D. S.
D. R.
0
5
10
15
CONTROL
POST-OP.
DRUGS

FIGURE 9

EFFECTS OF DRUGS ON POST-OPERATIVE DELAYED RESPONSE SCORES, ANIMAL LS-4

P = Phenidylate

W = Water

A = Amphetamine

M = Meprobamate

R = Reserpine

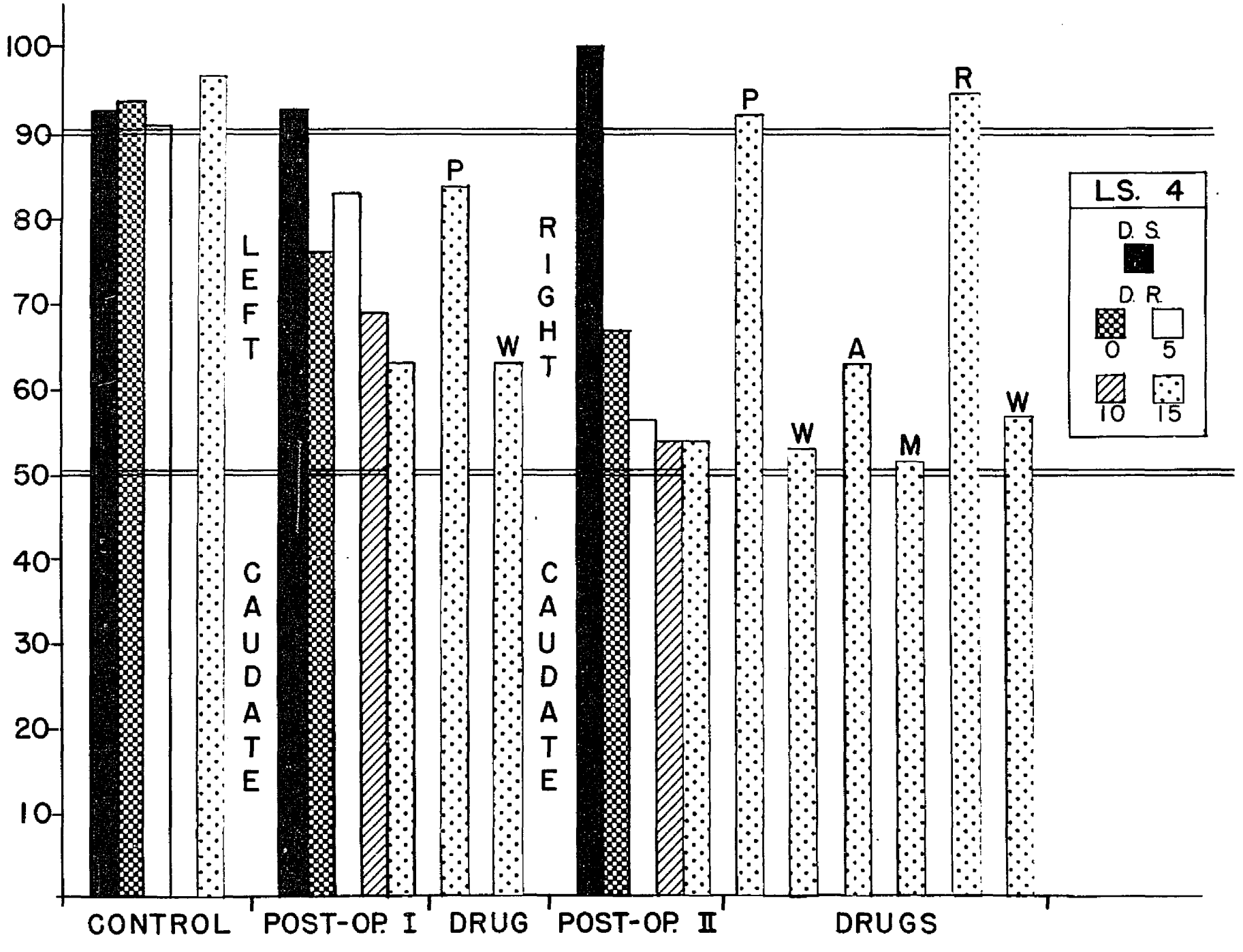

100
90
80
70
60
50
40
30
20
10
LEFT CAUDATE
RIGHT CAUDATE
P
W
P
W
A
M
R
W
LS. 4
D. S.
D. R.
0
5
10
15
CONTROL
POST-OP. I
DRUG
POST-OP. II
DRUGS

FIGURE 10

EFFECTS OF DRUGS ON POST-OPERATIVE DELAYED RESPONSE SCORES, ANIMAL LS-6

P = Phenidylate

W = Water

M = Meprobamate

R = Reserpine

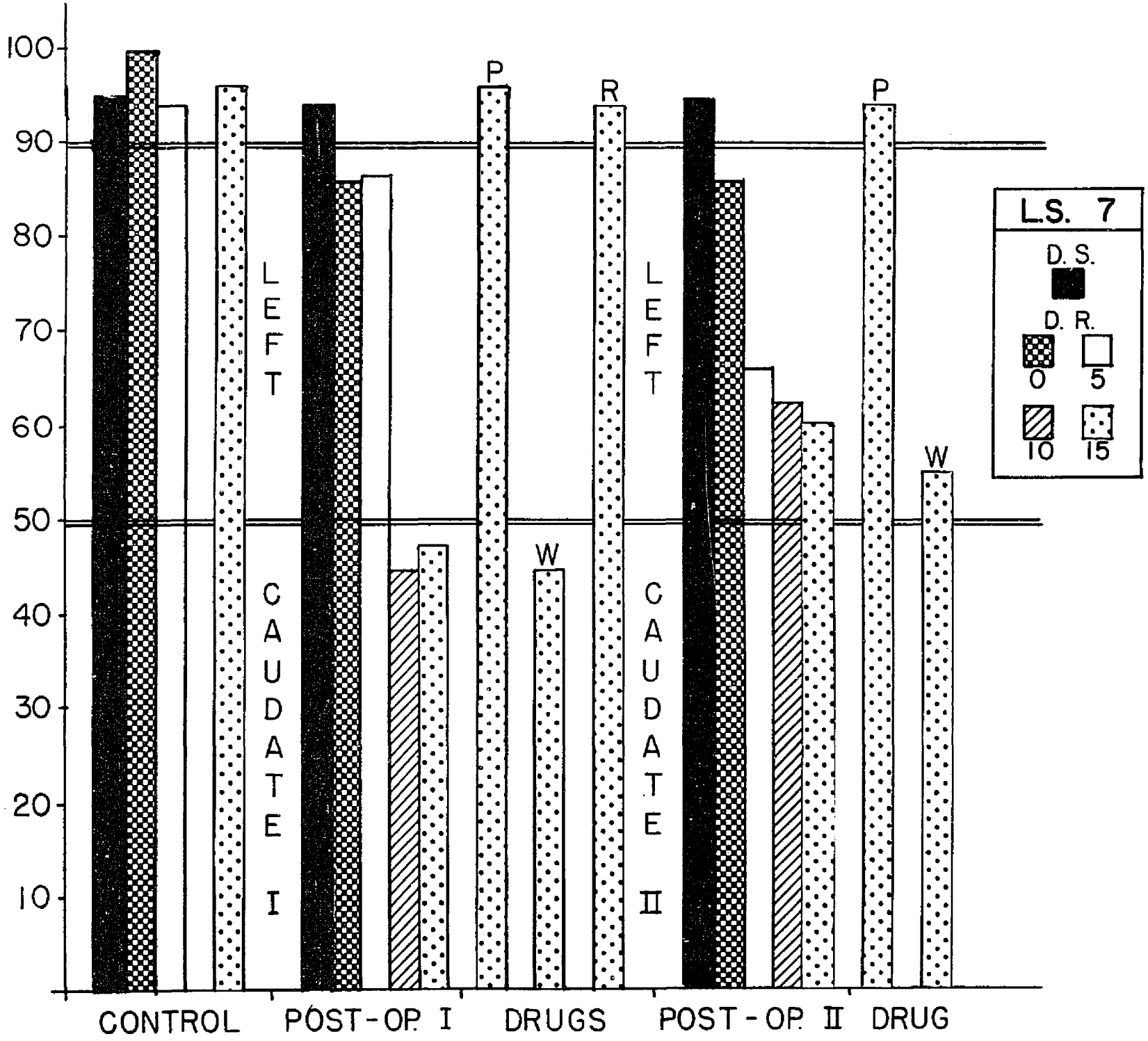
FIGURE 11

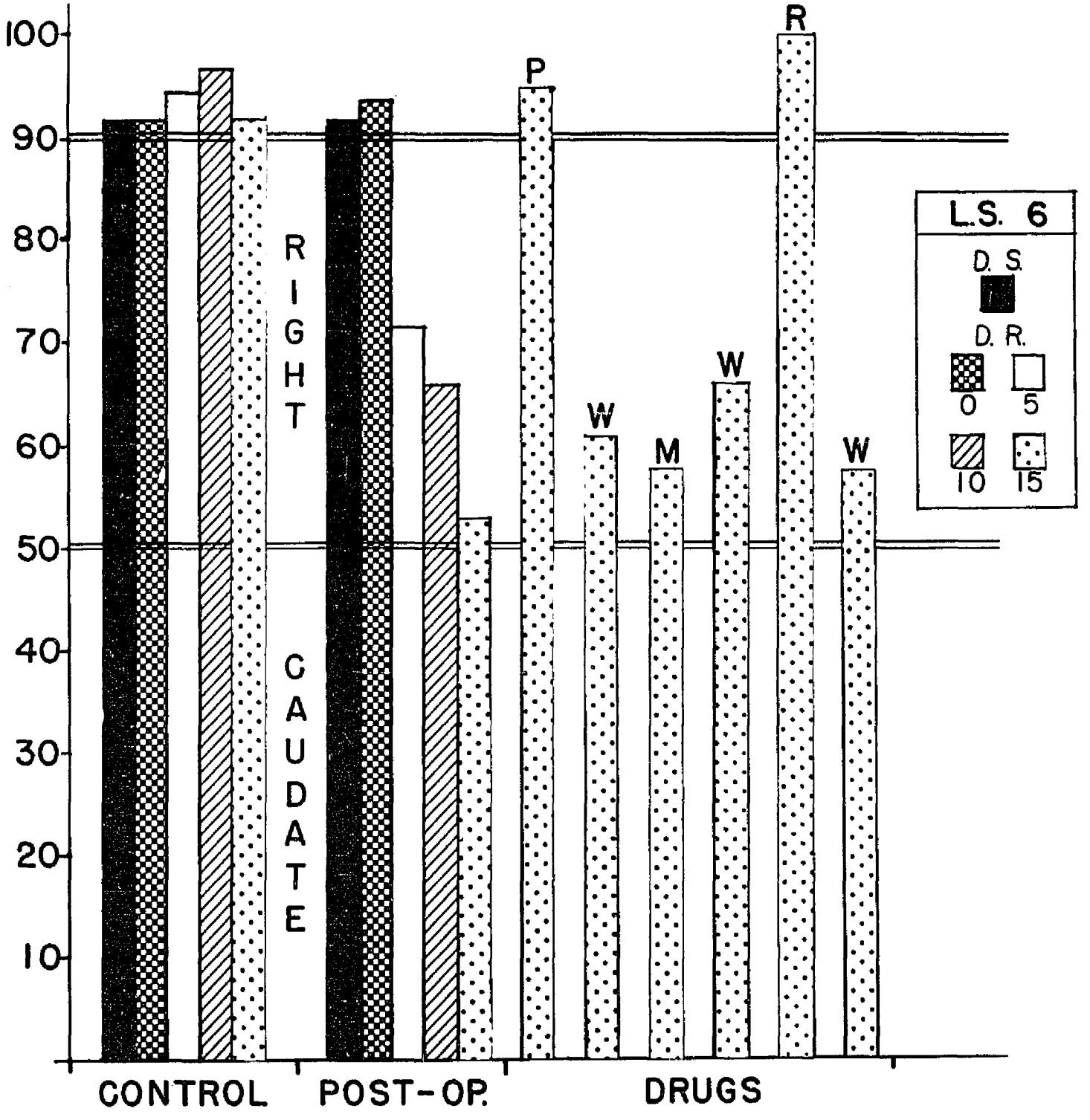
EFFECTS OF DRUGS ON POST-OPERATIVE DELAYED RESPONSE SCORES, ANIMAL LS-7

P = Phenidylate

W = Water

R = Reserpine


100
90
80
70
60
50
40
30
20
10
LEFT CAUDATE I
LEFT CAUDATE II
P
R
P
W
W
L.S. 7
D. S.
D. R.
0
5
10
15
CONTROL
POST-OP. I
DRUGS
POST-OP. II
DRUG


100
90
80
70
60
50
40
30
20
10
RIGHT
CAUDATE
P
W
M
W
R
W
L.S. 6
D. S.
D. R.
0
5
10
15
CONTROL
POST-OP.
DRUGS

C. QUALITATIVE BEHAVIOR CHANGES FOLLOWING DRUG TREATMENT

I. PHENIDYLATE

Affective changes. The post-operative monkey has been described as showing a flattening of affect. He seems indifferent to his surroundings, and reacts with little feeling to repeated failure and loss of reward in the psychological testing session. He is less interested in what goes on about him and seldom explores the testing cage as he did before operation. The caudate lesioned monkey accepts his fate with stoicism and neglects changes in the environment which once interested him.

Several interesting changes occur when phenidylate is given to such a monkey. The subject is likely to react in a quasi-aggressive manner. Such animals often charged the sides of their test cage and bared their teeth in an aggressive way. They often bit and chewed on the cage frame in a destructive way. The animal once again showed exaggerated interest in the things going on about him. Subjects were noted to jump and react with exaggerated leaps to noises. "Temper tantrums" sometimes occurred when testing was delayed for some reason or when the animal did not like the food in the goal boxes. Pre-response behavior, missing since the caudate operation, was restored and the monkey reacted to the cue with renewed interest. Random pacing was subjugated to the needs

of the test situation.

Drive level. Phenidylate given in moderate doses (0.25 - 0.5 mg./kg. body weight) did not seem to affect drive level very greatly. For example, one animal ran 100 consecutive trials of fifteen-second delayed response under phenidylate. None of the subjects refused to test with moderate phenidylate doses. The usual number of trials made under the drug compared favorably with the number of trials made on the best non-drug days. With larger phenidylate dosage, aggressive and other affective changes were much increased and the animal often refused to test. The monkey often refused to take food even when it was offered from open goal boxes. Fasting prior to test would not cause the animal under this dosage level of phenidylate to accept food. If effective drive level is defined as the number of trials run voluntarily by the animal in a single test session, then high phenidylate doses (above 0.5 mg./kg.) may be said to affect drive adversely.

Other changes. Additional changes in behavior have been noted during phenidylate influence which do not seem to bear directly on test performance. Monkeys who have been given phenidylate often chatter their teeth compulsively. Strange repetitive motor mechanisms sometimes appeared. An example of such a mannerism was seen in repetitive clinching of the hands. Fine hand tremors

were noted in several animals as they manipulated the goal boxes. Postural stance was sometimes exaggerated, and the monkey held himself erect in a tense and unnatural posture. Muscular coordination was often impaired. Intentional acts were accompanied by jerky movements of the hands and arms. The phenidylate treated animal occasionally had difficulty in opening the goal box lids because his hand overshot the edge of the box lid. Sometimes the animal had to be forced to let go of the food tray because he attempted to grip and hold onto it.

A main conclusion gained from observation of monkeys while they are under the influence of phenidylate is that the monkey is not acting in a normal manner. Phenidylate has the effect of restoring delayed response performance to normal levels, but this change is accompanied by behavior that is never seen in the normal animal.

II. RESERPINE

Affective changes. Changes in behavior occurring after Reserpine treatment seem less complex than the changes which occur after phenidylate treatment. Reserpine seems to have the opposite effect from phenidylate. Reserpine acts to sedate the animal; the subject becomes progressively more tranquil as treatment proceeds. His reaction to external stimulation slows and the animal becomes lethargic and withdrawn from

the environment. It was sometimes necessary to rap the test cage sharply to attract the animal's attention to a forthcoming test trial. Parkinsonian-like tremors in the hands and arms were sometimes noted after two or three days continued treatment. Response latency between test trials was often extended under Reserpine because the monkey took longer to respond when the tray containing the cue boxes was advanced to the feeding position. The animal was always able to move under his own power into the test cage, but it was sometimes necessary to force him to move.

Drive level. It is difficult to interpret the effect of Reserpine dosage on test motivation. When moderate doses were used, the animal was usually willing to test. However, test animals often averaged fewer trials under these conditions than when they were not under Reserpine influence. The effect of Reserpine on drive level seems to be a slow one, which allows opportunity to obtain valid test trials before the point is reached where all tests are refused.

As in the case of phenidylate, the animal under the influence of Reserpine does not act like a normal monkey. The increase in psychological test performance occurs while the animal is showing symptoms of a drugged nervous system. Such symptoms are never seen in the normal monkey.

D. IMPLICATIONS OF DRUG STUDIES IN DELAYED RESPONSE TESTING

A summary of the drug testing yields several conclusions. Of first importance is the fact that drugs were effective in restoring criterion level functioning on the fifteen-second delayed response test. This finding would seem to settle the argument that these animals have "lost" a specific mental ability which has been taught to them in the past. The present findings are in accord with the experiments of Wade and Pribram. The present experiment shows that the subjects have not lost the memory for the delayed response test. They are merely unable to perform correctly because of impairments introduced as an effect of nervous lesions. The fact that animals who performed fifteen-second delayed response at criterion levels under the drugs returned immediately to chance accuracy levels on the day following treatment is further evidence in this direction.

More difficult to interpret is the fact that two such different types of drugs as phenidylate and Reserpine are both effective in restoring delayed response performance. Both stimulants and sedatives seem effective in restoring delayed response performance. The apparent pharmacological action of the drug does not seem to be an important test determinant. Other agents besides drugs may act in this way. Testing in a darkened

room, fasting prior to test, and manipulation of the difficulty of the test by varied delay intervals are all examples of effective mechanisms which seem to work because they aid the animal in making all of the correct reactions which must be made before the final response.

The fact that small drug doses had no effect on hyperactivity which produced satisfactory test performance has interesting implications. This finding, along with others, supports the conclusion that post-operative hyperactivity and psychological test deficit are not cause and effect. If they were, drug doses which produced satisfactory test performance should also be effective in reducing hyperactivity. The fact that the same drugs are effective in both cases (but at different dosages) may mean that the drugs are acting on some as yet un-defined central mechanism which is responsible for both conditions.

CHAPTER V

RESULTS OF ADDITIONAL TESTS AND EXAMINATIONS

A. LOCOMOTOR HYPERACTIVITY AND ELECTROENCEPHALOGRAPHY FOLLOWING VARIOUS LESIONS

This section will discuss the effects of specific lesions on the activity of the monkeys. This data was obtained by pre- and post-operative series of tests conducted in the manner described in the methods chapter. The results of a number of individual testing sessions were summed to give an average hourly count of cage crossings before and after operation. Changes in the amount of activity shown in a unit time were noted, and variation in the patterns of this activity was also studied. The data concerning activity changes will be related whenever possible to changes in psychological test performance. This subject will be discussed at greater length in the discussion chapter, where all of the data of the study will be considered in a unified way.

A short summary of pertinent E.E.G. findings will also be included in this section, because this data relates to the wide range testing program used in the study of the experimental animals of the series.

LOCOMOTOR HYPERACTIVITY

BILATERAL SIMULTANEOUS CAUDATE LESIONS

The experimental monkey which received simultaneous caudate lesions, LS-2, experienced a loss of delayed response abilities and a change in the amount and pattern of activity. During the pre-operative period, LS-2 indicated upon repeated measurement that his activity was in the lower range of activity shown by normal animals. His activity was fairly stable from day to day and he showed almost a 2:1 preference for the top of the test cage.

His activity was immediately increased following caudate lesions. His activity was three times the normal average and two times the pre-operative maximum on the first post-operative day. All of this activity took place on the top of the cage and the monkey avoided the cage floor altogether. During the second to ninth post-operative days, activity increased until the average was twenty times the pre-operative average. All of this activity was confined to the top of the test cage. Activity changed again on the tenth post-operative day. Half of the animal's activity was on the floor of the cage on this day. From the eleventh post-operative day until the end of testing the subject stabilized at an activity level which was fifteen times the normal average. Approximately 2/3 of this activity was on the floor of the test cage.

BILATERAL FRONTAL CORTICAL LESIONS

Animal LS-3 received bilateral lesions to the mid-lateral frontal cortex in the region of sulcus principalis. No change in psychological test performance followed this operation. LS-3 proved to be a satisfactory animal for psychological test purposes but a highly unsatisfactory one in which to study activity. LS-3 was tested for activity during two months preceding psychological test training. Activity was within a stable normal range during this period. Activity measurements were not made for the next ten months because of a prolonged and difficult psychological training course. The animal was again tested for activity when it had mastered the psychological tests preparatory to operation. The monkey's activity had increased to 16 times the initial level and the variation in activity rates from day to day had become great. No real cause has been found for this monkey's great spontaneous change in activity level. One other animal in the study experienced a change in activity during training which was similar to the one found in this subject. Such changes in activity are sometimes seen as the result of infectious diseases. During the time of psychological training in this animal, a new monkey was introduced to the colony which had a very high spontaneous activity rate. The

possibility of a transmitted disease cannot be ruled out. The cortical operation produced no real change in this animal's activity. There was no change in the pattern of the monkey's activity; she still preferred the cage floor. The average rate of activity after operation was within the range of values found in the pre-operative subject.

TWO STAGE CAUDATE LESIONS

Animal LS-4 received two contralateral caudate operations. Delayed response performance changed after a unilateral ablation so that the monkey showed a partial loss of test function. The second caudate lesions on the opposite side produced more profound impairment of delayed response ability. LS-4 was also a very poor animal for the study of activity changes. Activity measurements were made prior to psychological test training which were in the low average range. Test training occupied an eight month period when no activity measurements were made. Activity measurements made prior to operation indicated a great increase in average rate with great variation from day to day. This spontaneous change occurred at exactly the same time as a similar change in LS-3's activity. Previous experience in testing activity of normal monkeys shows that spontaneous activity changes are very rare in the normal subject. Stability of rate

and pattern over long periods of time is the rule rather than the exception.

The first unilateral caudate lesions produced an activity change which was 1-1/2 times the post-operative normal average. No pattern change was seen on either the two or twenty-four hour tests.

The second operation produced no further increase in activity rate. The pattern of activity changed significantly. Activity at the top of the cage increased 6 times following the second lesions.

UNILATERAL CAUDATE LESIONS

Animal LS-6 received a unilateral ablation of the right caudate head. A partial loss of delayed response abilities and a change in the rate and pattern of activity followed this operation. LS-6 showed activity in the upper normal range before surgery. He had a 3.2 preference for the top of the test cage. Activity was almost zero on the first post-operative day. LS-6 averaged ten crossings per hour on the top of the cage through the eighth post-operative day. Activity was zero on the bottom of the cage. LS-6 showed a preference for the top of the cage for the remaining test days and he stabilized at an average activity level which was essentially unchanged from preoperative findings in the two hour cage.

The post-operative activity in the twenty-four hour cage was very unusual. From 9:00 a.m. to 2:00 p.m. the animal's activity was very slow. From 2:00 p.m. to lights out at 6:00 p.m. the activity reached very high levels. Indeed, the late afternoon activity was on the order of seven times the pre-operative normal level. This is an unusual finding, and is not normally expected in lesioned monkeys. Two hour activity tests were almost all taken in the morning or early afternoon where the animal is known to have been lethargic. Therefore the twenty-four hour activity measurements are more valid as indicators of activity change in LS-6 than the shorter tests.

SEQUENTIAL UNILATERAL CAUDATE LESIONS

Animal LS-7 received two operations on the left caudate region. Psychological performance on the delayed response test was impaired after the first operation, but slow improvement in test accuracy resulted after the second operation. LS-7 indicated middle normal levels of activity before the operations. The normal animal was very unstable in activity tests from day to day and the range of measured activity under the same conditions was very great. LS-7 showed no preference for either the top or the bottom of the cage.

Activity was increased two and one-half times after the first caudate operation. Activity level was unstable

in daily testing and the subject showed a 2:1 preference for the bottom of the test cage (i.e. a change in pattern of activity). Activity rate decreased an average of 20% following the second ipsilateral caudate operation. The rate became very variable from day to day and the monkey showed an even stronger 3:1 preference for the bottom of the test cage.

It should be noted that activity changes followed the expected pattern after the first operation in this animal. The same expected pattern was established in psychological testing made at the same time. Both activity and psychological test behavior were not as expected following the second operation. These unexpected developments correlate well with the findings of the histological study of this animal's brain which are discussed in chapter VI.

ELECTROENCEPHALOGRAPHY

No consistent electroencephalographic changes were seen in any of the animals with caudate lesions. This is not surprising in view of the comparatively small extent of the destruction. The frontal decorticate monkey had an electroencephalogram in which the voltages recorded over the frontal poles were somewhat reduced. The record was otherwise unremarkable. The latter findings are consistent with general experience in cortical removals.

No prior reports exist on the electroencephalogram following this type of caudate damage.

B. HISTOPATHOLOGY OF EXPERIMENTAL LESIONS

Much of the theoretical knowledge about various parts of the central nervous system has been contributed by clinical workers who have been careful observers as well as physicians interested in helping a diseased human being. Much of this knowledge has been gained through the correlation of the symptomatology of the patient with anatomical abnormalities found at post-mortem examination. In experimental work, the attempt is made to add precision to this process which would never be possible if one had to rely on chance factors to provide the physiological preparations. In experimental neurology the damage is intentional rather than accidental but the same procedures of correlation of behavior changes with anatomical structure must be employed. If an experimental study is to have value, one must be able to certify which structures were damaged and which were left intact. It is rare that the intentional lesion planned by the surgeon is exactly accomplished. Totally erroneous conclusions may be formed unless the exact extent of injury is known. This information can only be gained through extensive histological examination of the tissues involved.

All five brains were subjected to histological examination in the present study. Four of these brains had at least some caudate damage, and one did not.

HISTOLOGICAL METHODS

Sacrifice of the monkeys was begun with a deep barbiturate anaesthesia. The chest wall was opened, and the heart was incised to allow perfusion with saline followed by 10% formalin solution. The brain was removed and placed in formalin.

When hardening was accomplished, the brain was washed and run through successively increasing concentrations of alcohol, ending in a bath of alcohol and ether. Embedding was accomplished in nitrocellulose for four of the animals. One animal's brain was embedded in paraffin because this procedure is more rapid than the nitrocellulose method.

Serial sections were cut at 25 microns in most animals. In some cases sections were thinner or thicker than this because of technical problems associated with the sectioning procedure. Every tenth section was saved, and every second saved section was stained with a modified windle nissl technique. Each nissl section was one-half millimeter from the succeeding one. In general, the three sections representing the most anterior, middle, and most posterior limits of the lesion area were used in the illustrations of the lesion.

For the illustrations, the sections were projected with a photographic enlarger and drawn. Brain substance showing changes in the area of lesions is shown in black whether it involved white or gray substance. Damage to the frontal cortex is shown as a heavy line.

ANALYSIS OF THE LESIONS

LS-2. This monkey received bilateral caudate lesions in a single operation. The caudate lesions in this animal are accurately located and fairly equal on both sides (Fig. 12). Serial sections through the greatest extent of these lesions show that some damage to structures surrounding the caudate has occurred on both sides. Both the right and left lesions include a very small amount of internal capsule tissue. The right lesion includes slightly more putamen tissue than the left lesion. Both lesions however, impringe on only the very frontal tip of the putamen. The major area involved by these lesions is limited to the caudates. Needle tracks are clean and there is a minimal damage of cortical tissue overlying the lesion areas.

LS-3. This monkey received a simultaneous bilateral midlateral frontal decortication. The left lesion is larger than the right. Sulcus arcuatus marks the posterior limit of the main lesions, but a tip of the left lesion extends slightly medial and posterior to this point.

FIGURE 12

LESION RECONSTRUCTION, ANIMAL LS-2

1. Anterior limit of lesions
2. Section showing greatest damage
3. Posterior limit of lesions

L.S. 2

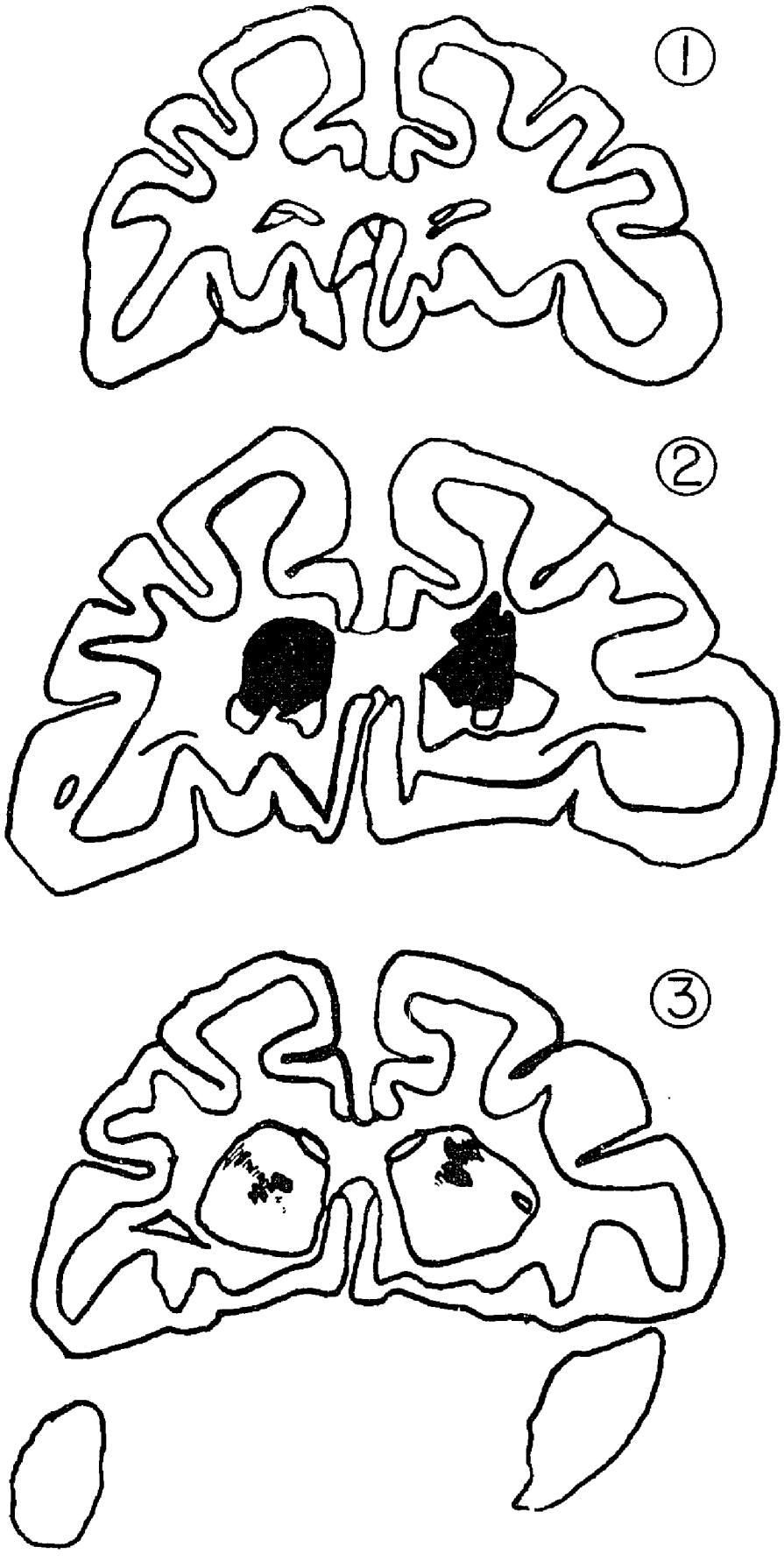
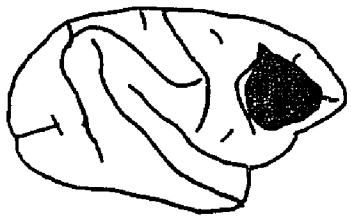


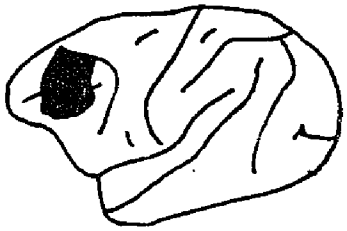
FIGURE 13

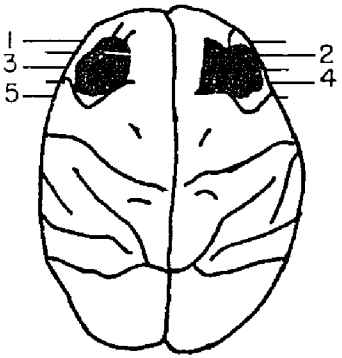
LESION RECONSTRUCTION, ANIMAL LS-3

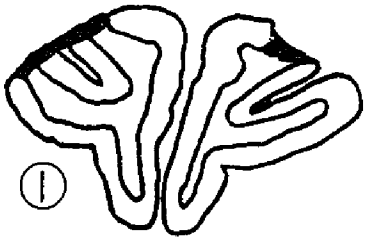
Cross sections as indicated

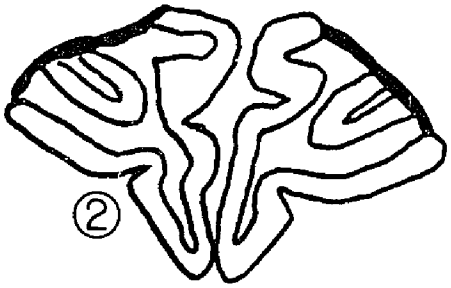
L.S. 3

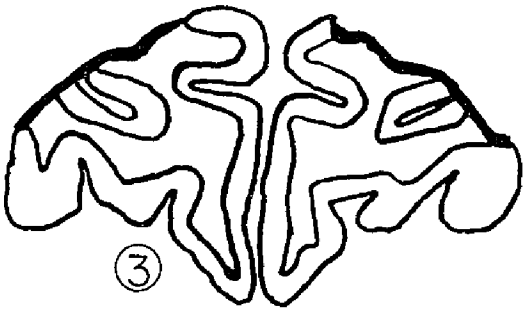


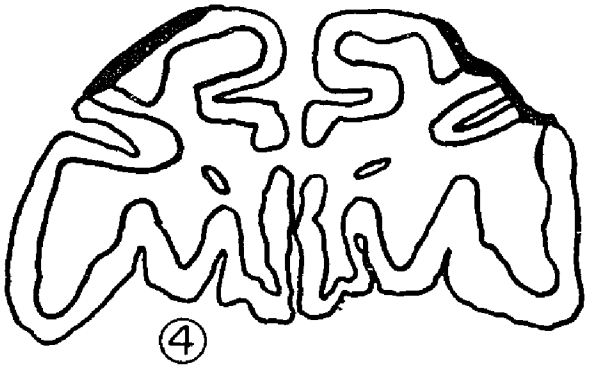


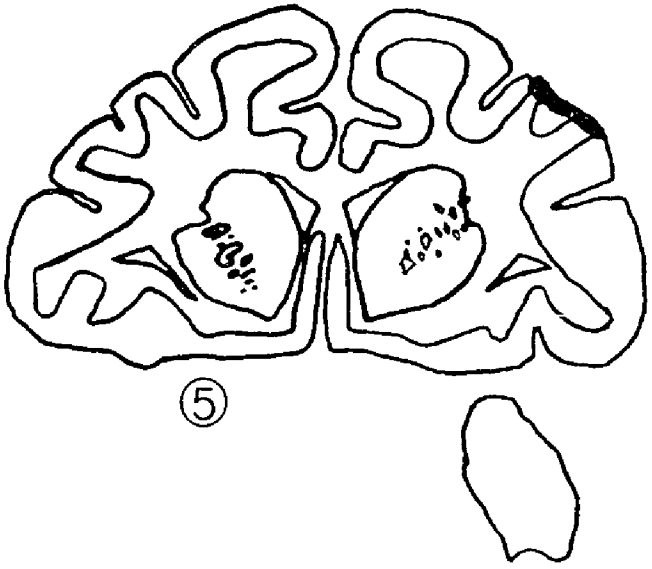












Little or no cortex is removed from the depths of sulcus principalis. Lesions are extremely clean and there is no evidence of any involvement of subcortical tissue in the corpus striatum (Fig. 13). Thalamic sections were not drawn, but examination of these sections indicates well differentiated degenerative loss and glial reaction in thalamic nucleus medialis dorsalis. Degeneration of medialis dorsalis has been invariably reported after cortical lesions in the midlateral frontal cortex. Even the smaller of the two lesions appears to include the areas cited by previous workers as essential for the delayed-response ability.

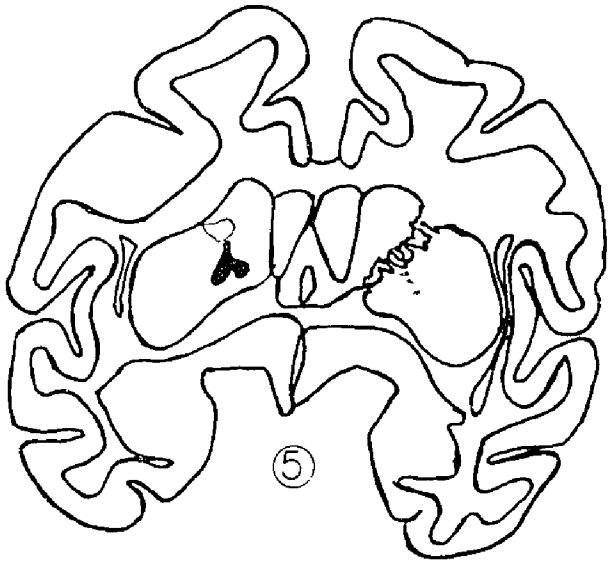
LS-4. This monkey received bilateral caudate lesions in two stages. The left lesion was the first done and was placed slightly more anterior than the right lesion. Involvement of caudate tissue is great on both sides with only slight involvement of surrounding structures. The serial sections indicate the greatest extent of both lesions with some minimal damage to the internal capsule and putamen on both sides (Fig. 14). Needle tracks are clean and essentially no cortical damage is indicated overlying the damaged areas. As amatter of fact, three of the six needle punctures could not be located with certainty upon gross examination of the cortex.

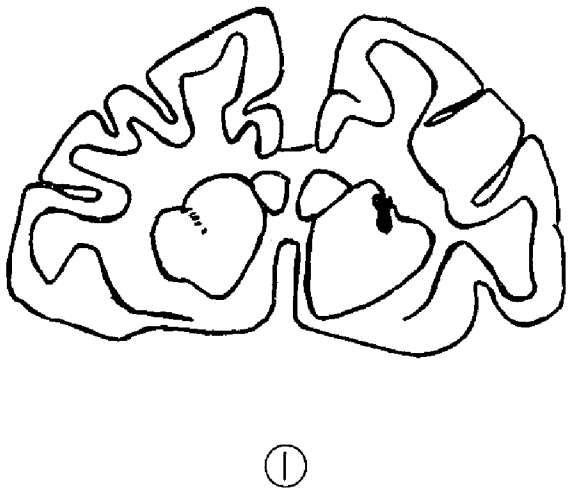
FIGURE 14

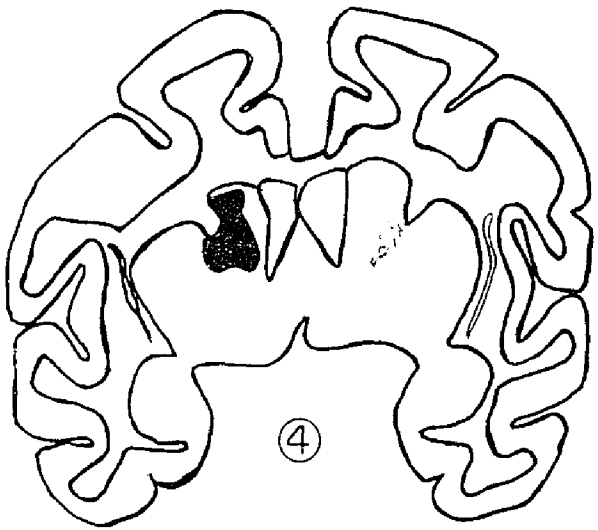
LESION RECONSTRUCTION, ANIMAL LS-4

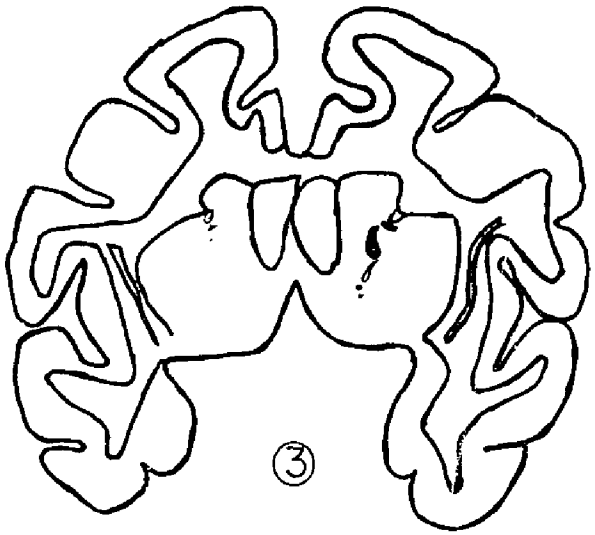
1. Anterior limit of left caudate lesions
2. Section showing greatest left caudate damage
3. Posterior limit of left caudate lesions and anterior limit of right caudate lesions
4. Section showing greatest right caudate damage
5. Posterior limits of right caudate lesions

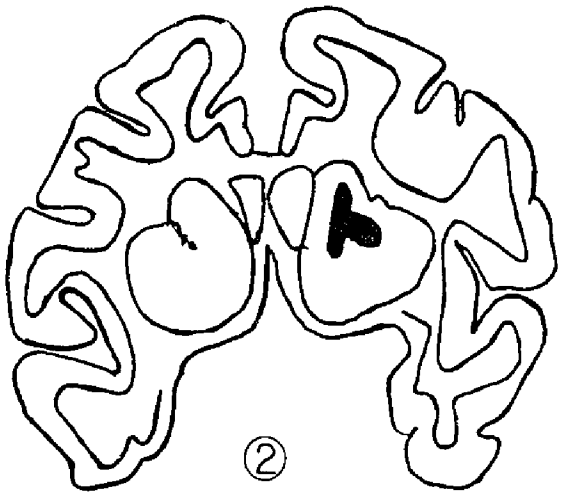
L.S. 4











LS-6. This monkey received a single operation which damaged the right caudate. The damage at its greatest extent is well confined to the caudate nucleus (Fig. 15). No damage was seen in the internal capsule, putamen, or in structures surrounding the corpus striatum. The anterior sections of this lesion were lost due to technical problems associated with histological preparation.

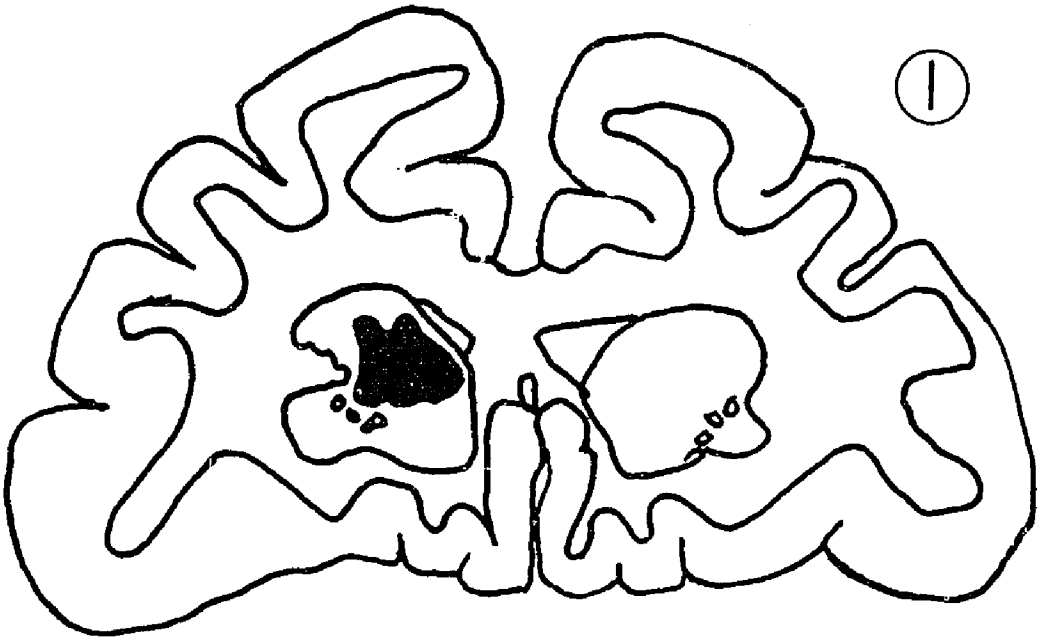
LS-7. This monkey received two operations at different times on the left hemisphere. The first lesion is well placed in the left caudate head with little internal capsule and putamen damages (Fig. 16). The second lesion is medial and posterior to the first one and includes almost no caudate tissue (Fig. 16). The areas most damaged by this operation include the corpus collosum and lateral ventricle. Errors in placement of this second lesion seem to have resulted in almost no damage to the caudate nucleus and great damage to surrounding white matter. This animal had an unusually large and aberrantly shaped skull, and coordinate lesion placement was extremely difficult.

FIGURE 15

LESION RECONSTRUCTION, ANIMAL LS-6

1. Section showing greatest damage
2. Posterior limits of lesion

L.S. 6



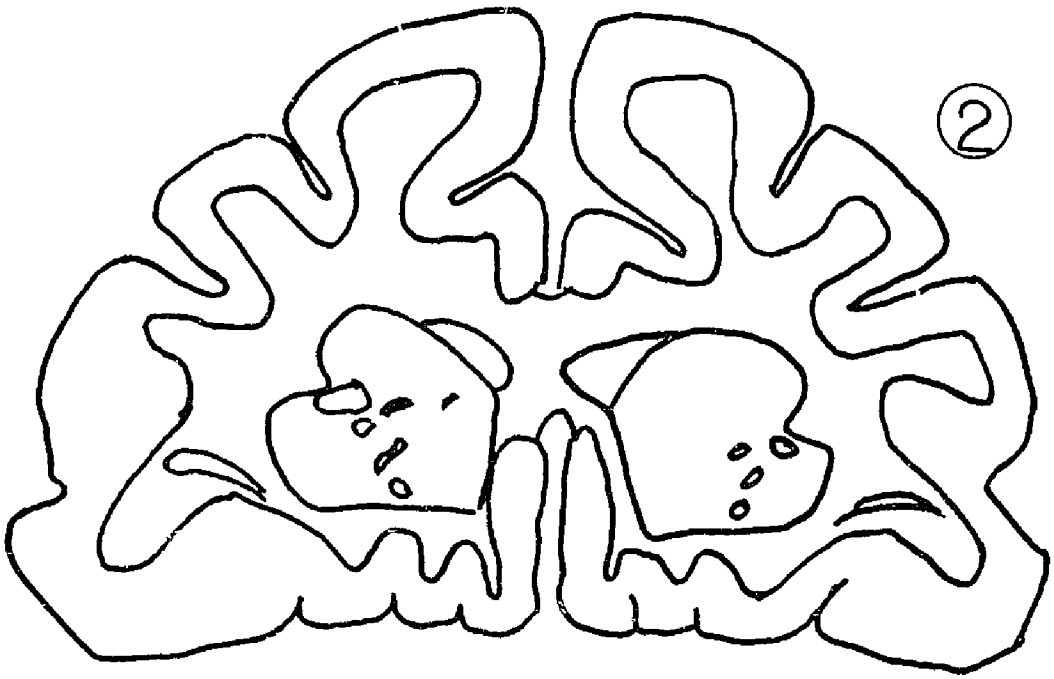
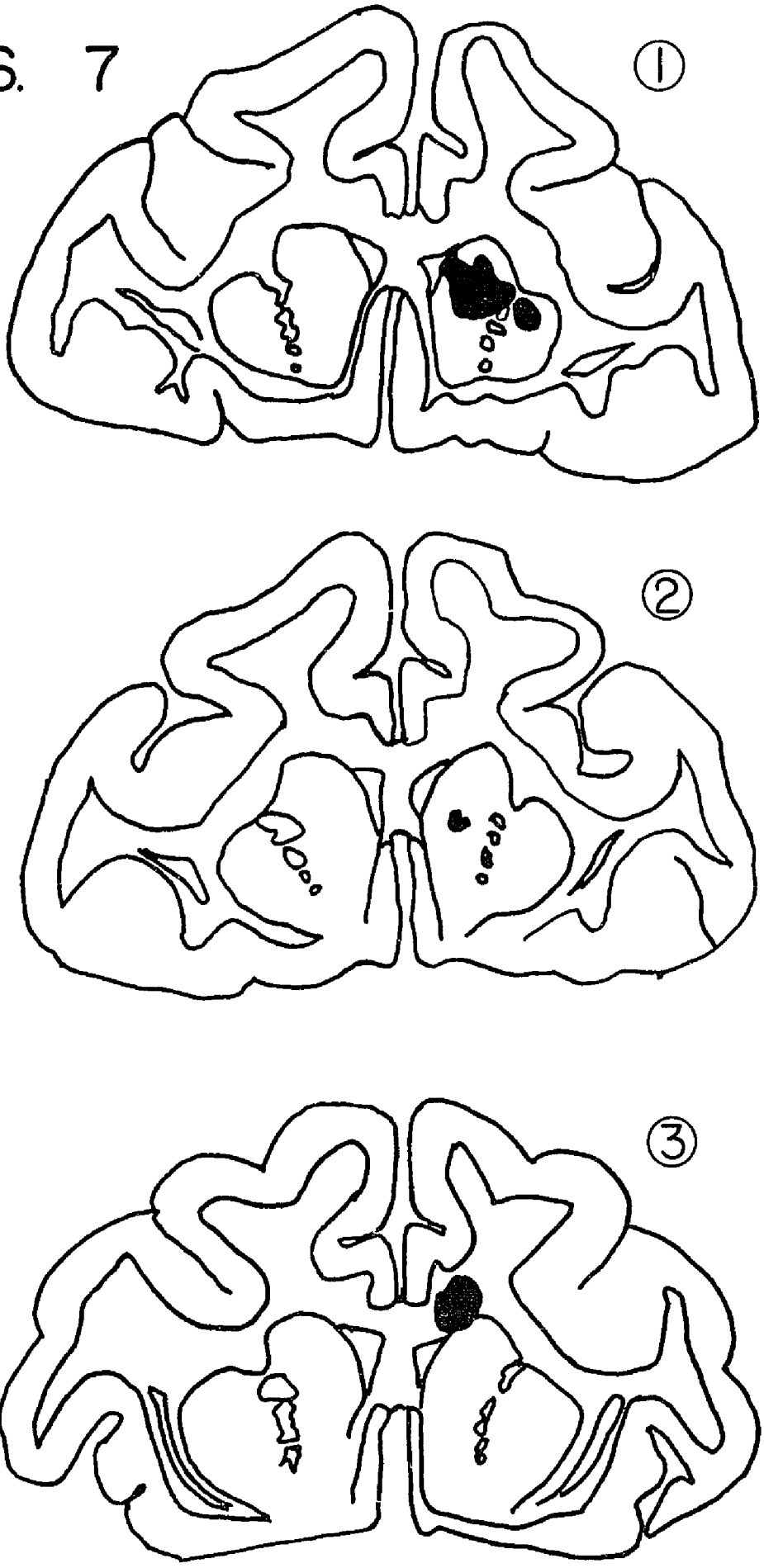


FIGURE 16

LESION RECONSTRUCTION, ANIMAL LS-7

1. Section showing greatest left caudate damage, first lesions
2. Anterior limits of first lesions
3. Section showing greatest extent of second lesions

L.S. 7



CHAPTER VI

DISCUSSION

CHAPTER VI

DISCUSSION

The purpose of this experiment was to study behavioral changes which occurred after sterotaxic lesions in the caudate nuclei of four rhesus monkeys. These behavioral changes are very similar to the changes which have been described by other workers who have studied frontal lobe lesions in monkeys and men. Selective loss of delayed response abilities has been found in monkeys with caudate lesions. Very small sub-cortical caudate lesions have produced a loss in delayed response abilities which is as profound as the loss described by other investigators who performed gross ablations or removals of both frontal lobes.

Histological examinations conducted at the conclusion of this experiment have shown that the magnitude of delayed response deficit is related to the amount of caudate tissue damaged. The first animal in the present series, LS-2, showed a complete and permanent loss of delayed response after an operation which bilaterally destroyed a well localized area in both caudate heads. This same animal retained the ability to perform color discriminations while showing many other behavioral changes which are considered typical of the animal with lesions of the frontal lobes.

Further proof of the intimate role of the caudate

nuclei in delayed response tasks is the partial loss of test function which followed less extensive unilateral caudate lesions. Animals LS-4, LS-6, and LS-7 showed this identical partial loss of test function after unilateral caudate lesions. The delayed response test is a sensitive behavioral measurement which indicates lost function even after these very small and discrete caudate lesions. This partial loss was further extended to a complete loss of test function when a second contralateral caudate operation was performed. The present study has failed to establish whether bilateral caudate lesions are necessary for complete loss of delayed response abilities. The attempt to produce unilateral caudate lesions which were comparable in total size to the tissue damage produced in bilateral lesions failed in the last animal of the series because of misplacement of the second lesion.

A further aim of the present study was to define the underlying mechanism of delayed response deficit in caudate-lesioned animals. This becomes a particularly important thing when one considers the intimate relationship between caudate lesions and test scores. The wide scope of behavioral changes which occur after caudate lesions will be examined in detail in order to define important factors affecting test performance.

Monkeys with caudate lesions did not lose the ability to perform a simple color discrimination test. A comparison of delayed response and discrimination tasks is of value in understanding this phenomenon. The cues for correct response in the color discrimination test are present at the time of response. The monkey merely observes the yellow box and opens it to obtain food. This positive response to the yellow marker has been "stamped in" through long preoperative training. Each new test trial requires no new adjustment but merely repeats an old experience exactly. The cue for correct response is always present in the external environment at the critical time.

The delayed response task introduces a delay interval between the cue presentation and the later opportunity to respond. The monkey no longer has any cue to help him respond correctly once the delay interval has been introduced. After the pre-response cue the animal must <u>form</u> some kind of memory trace in order to attain the correct goal. This process must come about through observation of the examiner's actions during the period of cue presentation. The subject must therefore attend to significant cues in the environment which are only briefly presented to him.

A possible explanation for the caudate operate's failure to appreciate momentary cues from the environment

relates to the hyper-kinesia which is often shown by these animals. Excess and uncontrolled motor activity may occupy the monkey so much that he neglects subtle environmental cues. The data of the present experiment has not supported this hypothesis. The same type of caudate operations did not produce the same degree of activity change in all subjects. The behavioral changes shown by standard behavioral tests were much more consistent from animal to animal than were activity changes. The monkey whose lesions were limited to the midlateral frontal cortex was made somewhat hyperactive by the operation, but there was no change in test performance. The evidence from drug testing experiments also supports the conclusion that hyperactivity and delayed response deficit are not directly connected. Both excitant and sedative drugs have been effective in reducing hyperactivity and restoring test function in monkeys with caudate lesions. Phenidylate was effective in very small dosages where psychological test performance was concerned. Doses of the same magnitude had no effect on activity. This fact supports the interpretation that the excitant and sedative drugs worked on a common mechanism which brought about both hyperactivity and delayed response deficit.

The subject's pre-response behavior has been another subject under investigation. Careful observations were

made of pre-response behavior. These observations are described in detail in the results chapter. In general, pre-response behavior was noted at cue presentation when the animal was performing the delayed response correctly. There seems no reasonable doubt that a strong pre-response aids the animal's performance. However, the present series of experiments negates the hypothesis that correct pre-response always means that a correct delayed response will follow after delay. This conclusion has been advanced by other experimenters who noted complete loss of both delayed response and pre-response behavior after frontal lesions. The partial loss of delayed response found in the present study does not support this interpretation. Partial loss of delayed response was shown in the present study when the lesioned monkey indicated criterion level accuracy on short delay intervals and chance accuracy scores on longer delay intervals. This is a new finding in delayed response work which calls for a re-interpretation of pre-response theories. The testing monkey has no knowledge that the delay interval will be varied. The monkey who shows pre-response behavior at short delay intervals has demonstrated his ability to perform this response to cue.

Daily observation of monkeys after caudate operations has indicated a loss of interest in the external

environment, a reduction of test motivation, and a general reduction of "emotional" responses. These factors appear to relate to post-operative test performance under certain conditions. These changes were most frequently observed in animals with extensive caudate damage. These same animals were not capable of delayed response performance under usual conditions. In these cases the monkeys regressed to a very primitive solution of the delayed response problem. They reacted with position habits for extended periods and showed no frustration at receiving reward on a chance basis. They seemed to "give up" and accept the easiest solution possible. Manipulation of food intake had no effect on test accuracy. Loss of emotional interest seems an important factor, particularly when the monkeys were tested on massed trials of delayed response at a uniform delay interval. The injured monkey may simply give up and regress to chance behavior when the test is too hard for him. Motivation is sufficient to complete the reaction chain only when the order of difficulty is below a critical point. Refusal to test may result under these conditions.

Examination of the summated delayed response data of monkeys with partial delayed response loss shows that accuracy of performance decreases as the length of the

period of delay is increased. In all three monkeys a sharp decline in accuracy occurred between five and fifteen seconds delay. Since the subject has no prior knowledge about the length of forced delay, difficulty during the period of delay must occur.

Another trend exists in the accuracy scores of partial loss monkeys. Partial loss monkeys were often tested on the same test day with groups of ten trials of the various delay intervals. An additional tabulation of these scores has been made in order to study the effect of suddenly varied delay interval on test accuracy. Three test subjects were considered who performed the five second delayed response and failed the fifteen second one. The results of this tabulation show that when a satisfactory five second test series is followed by fifteen second series there is no tendency for correct response on the initial fifteen second trial. Right and wrongs on the first fifteen second trial after a five second series of trials are almost equally distributed for all three subjects.

A similar tabulation was made of mixed test series in partial loss monkeys where fifteen second tests were given immediately before five second tests. The three partial loss monkeys show a 7 to 1 tendency to score correctly on the first five second trial when this trial has been given following a series of fifteen second tests performed at chance accuracy.

These results are not explained by any of the hypotheses which have been advanced in this chapter. The difficulty of the delayed response test itself, aside from the animal's previous experience, would seem to be the important variable in this case. The classical memory defect described by Jacobsen (1936) would seem the most parsimonious explanation. Monkeys fail the first trial in the fifteen second series or accomplish the first trial in the five second series in accordance with their ability to span the period of delay with a correct memory.

SUMMARY

The present experiments may be summarized as follows:

1. Restricted bilateral caudate lesions are followed by a specific loss of learned abilities (delayed response).

2. Caudate lesions produce no change in color discrimination ability, and thus the basic ability of the animals to respond in the test situation is not impaired.

3. Unilateral lesions of the caudate result in partial loss of delayed response ability.

4. Laterality of unilateral lesions makes no difference, regardless of the subject's handedness.

5. The excitant drug Ritalin restores delayed

response as does the sedative drug Reserpine, but more effectively.

6. Difficulty in spanning the period of delay with a correct memory of the cue is an important mechanism in delayed response deficit.

7. Difficulties in making proper pre-responses to cue, decreased interest in the environment, and decreased emotional responses are seen in caudate lesioned monkeys. These changes are also seen after gross frontal lesions in which large amounts of tissue has been damaged or destroyed. These changes serve to make delayed response more difficult for the subject.

8. Correlation between anatomical damage to the caudate and loss of delayed response abilities is good.

9. Damage or destruction of caudate nuclear tissue results in widespread quantitative and qualitative disturbances in behavior. Loss of delayed response ability is but a single aspect of this change.

BIBLIOGRAPHY

BLUM, JOSEPHINE S., CHOW, K. L., AND BLUM, R. A., 1951. Delayed response performance of monkeys with frontal removals after excitant and sedative drugs. J. Neurophysiol., 1951, 14, 197-202.

BLUM, R. A., 1948. The effect of bilateral removal of the prefrontal granular cortex on delayed response performance in the chimpanzee. Amer. Psych., 1948, 3, 237-238.

BLUM, R. A., 1952. Effects of subtotal lesions of frontal granular cortex on delayed response in monkeys. Arch. Neurol. and Psychiat., 1952, 67, 375-386.

BRESHAW, B., BARRERA, S. E., AND WARDEN, C. J., 1934. The effect of removal of the postcentral convolution in the Rhesus monkey on the delayed response. J. comp. Psych., 1934, 18, 207-226.

CAMPBELL, R. J., AND HARLOW, H. F., 1945. Problem solution by monkeys following removal of the prefrontal areas. V. Spatial delayed response. J. exp. Psych., 1945, 35, 110-126.

CARPENTER, C. R., AND NISSEN, H. W., 1934. An experimental analysis of some spatial variables in delayed response of chimps. Psych. Bull., 1934, 31, 689-693.

CHOW, K. L., 1954. Lack of behavioral effects following destruction of some thalamic association nuclei in monkey. Arch. Neurol. and Psychiat., 1954, 71, 762-771.

CHOW, K. L., AND HUTT, P. J., 1953. The association cortex of Macaca Mulath: A review of recent contributions to its anatomy and functions. Brain, 1953, 76, 625-667.

COWLES, J. T., 1939. A direct comparison of three methods of delayed response. Psych. Bull., 1939, 36, 598-601.

COWLES, J. T., 1941. Discrimination learning of pre-delay reinforcement in delayed response. Psych. Rev., 1941, 48, 225-234.

DAVIS, G. D., 1957. Effects of central excitant and depressant drugs on locomotor activity in the monkey. Amer. J. Physiol., 1957, 188, 619-623.

FINAN, J. L., 1939. Effects of frontal lobe lesions on temporally organized behavior in monkeys. J. Neurophysiol., 1939, 2, 208-226.

FINAN, J. L., 1940. An analysis of frontal lobe function in monkeys by means of two delayed response methods. Psych. Bull., 1940, 37, 496-497.

HARLOW, H. F., AND DAGNON, J., 1942. Problem solution by monkeys following bilateral removal of the prefrontal areas. J. exp. Psych., 1942, 32, 351-356.

HARLOW, H. F., AND SPAET, T., 1943. Problem solution by monkeys following bilateral removal of prefrontal areas. J. exp. Psych., 1943, 33, 500-507.

HARLOW, H. F., VEHLING, H., AND MASLOW, A. H., 1932. Comparative behavior of primates I. Delayed response tests on primates from lemur to orangoutan. J. comp. and physiol. Psych., 1932, 13, 313-336.

HARMON, P. J., TANKARD, MALEVA, HOVIDE, C., AND METTLER, F. A., 1954. An experimental anatomical analysis of the topography and polarity of the caudate-neocortex interrelationship in the primate. Anat. Rec., 1954, 118, 307-308.

JACOBSEN, C. F., 1931. A study of cerebral functioning in learning. The frontal lobes. J. comp. Neurol., 1931, 52, 271-340.

JACOBSON, C. F., 1935. Functions of frontal association areas in primates. Arch. neurol. and Psychiat., 1935, 33, 558-569.

JACOBSON, C. F., 1936. Studies of cerebral function in primates I. Function of the frontal association areas in monkeys. Comp. psych. Monogr., 1936, 13, 61-65.

JACOBSEN, C. F., AND ELDER, J. H., 1936. Studies of cerebral function in primates II. The effect of temporal lobe lesions on delayed response in monkeys. Comp. psych. Monogr., 1936, 13, 61-65.

JACOBSEN, C. F., AND HASLERUD, G. M., 1936. Studies of cerebral function in primates III. The effect of motor and premotor area lesions on delayed response in monkeys. Comp. psych. Monogr., 1936, 13, 66-68.

JACOBSEN, C. F., AND NISSEN, H. W., 1937. Studies of cerebral function in primates IV. The effects of frontal lobe lesions on the delayed alternation habit in monkeys. J. comp. Psych., 1937, 23, 101-102.

MAGOUN, H. W. Personal communication.

MALMO, R. B., 1942. Interference factors in delayed response in monkeys after removal of the frontal lobes. J. Neurophysiol., 1942, 5, 295-308.

METTLER, F. A., HOVIDE, C., AND GRUNDFEST, H., 1952. Electrophysiologic phenomena evoked by electrical stimulation of the caudate nucleus. Fed. Proc., 1952, 11, 107.

MEYER, D. R., HARLOW, H. F., AND SETTLEGE, P. H., 1951. A survey of delayed response performance by normal and brain damaged monkeys. J. comp. and physiol. Psych., 1951, 44, 17-25.

MISHKIN, M., 1957. Effects of small frontal lesions on delayed alternation in monkeys. J. Neurophysiol., 1957, 20, 615-621.

MISHKIN, M., AND PRIBRAM, K. H., 1956. Analysis of the effect of frontal lesions in the monkey II. Variations of delayed response. J. comp. and physiol. Psych., 1956, 49, 36-40.

PETERS, R. H., ROSVOLD, H. E., AND MIRSKEY, A. F., 1956. The effect of thalamic lesions upon delayed response type tests in the Rhesus monkey. J. comp. and physiol. Psych., 1956, 49, 111-116.

PRIBRAM, K. H., 1950. Some physical and pharmocological factors affecting delayed response performance of baboons following prefrontal lobotomy. J. Neurophysiol., 1950, 13, 373-382.

PRIBRAM, K. H., CHOW, K. L., AND SEMMES, JOSEPHINE, 1953. Limit and organization of the cortical projection from the medial thalamic nucleus in monkey. J. comp. Neurol., 1953, 98, 433-448.

PRIBRAM, K. H., AND MISHKIN, M., 1955. Analysis of frontal lesions in the monkey III. Object alternation. J. comp. and physiol. Psych., 1956, 49, 41-45.

PRIBRAM, K. H., MISHKIN, M., ROSVOLD, H. E., AND KAPLAN, S. J., 1952. Effects on delayed response performance of lesions of dorsolateral and ventrolateral frontal cortex of baboons. J. comp. and physiol. Psych., 1952, 45, 565-575.

ROSVOLD, H. E., AND DELGADO, J. M. R., 1956. The effect on delayed-alternation test performance of stimulating or destroying electrically structures within the frontal lobes of the monkey's brain. J. comp. and physiol. Psych., 1956, 49, 365-372.

SIMPSON, M. M., AND HARLOW, H. F., 1944. Solution by Rhesus monkeys of a nonspatial delayed response to the color or form attributes of a single stimulus. J. comp. Psych., 1944, 37, 211-220.

WADE, MARJORIE, 1947. The effects of sedatives on delayed response in monkeys following removal of the prefrontal lobes. J. Neurophysiol., 1947, 10, 57-61.

WADE, MARJORIE, 1952. Behavioral effects of prefrontal lobectomy, lobotomy and circumsection in the macaca mulatta monkey. J. com. Neurol., 1952, 96, 179-207.

WALKER, A. E., 1938. The primate thalamus. Chicago: University Chicago Press, 1938, xxiii, 321 pp.

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April 16, 1958